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(21) International Application Number: PCT/US00/02518 (22) International Filing Date: 22 February 2000 (22.02.00) (30) Priority Data: 09/256,948 24 February 1999 (24.02.99) US (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Department, 5200 Old Orchard Road, Skokie, IL 60077 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BARTA, Thomas, E. [US/US]; 1133 Maple Avenue, Evanston, IL 60202 (US). BECKER, Daniel, P. [US/US]; 1800 Maplewood Lane, Glenview, IL 60025 (US). BEDELL, Louis, J. [US/US]; 1832 E. Camp McDonald Road, Mt. Prospect, IL 60056 (US). BOEHM, Terri, L. [US/US]; 928 Cleta Drive, Ballwin, MO 63021 (US). CARROLL, Jeffery, N. [US/US]; 13 Cheshire Court, Collinsville, IL 60223 (US). DE CRESCENZO, Gary, A. [US/US]; 7345 Spruce Hill Court, St. Charles, MO 63304 (US). FOBIAN, Yvette, M. [US/US]; 1260 Fiddle Creek Road, Labadie, MO 63055 (US). FRESKOS, John, N. [US/US]; 7572		York, Clayton, MO 63105 (US). GETMAN, Daniel, P. [US/US]; 66 Sunny Hill Court, Chesterfield, MO 63017 (US). MCDONALD, Joseph, J. [US/US]; 1036 Johanna Drive, Ballwin, MO 63021 (US). HANSON, Gunnar, J. [US/US]; 7410 Keystone Avenue, Skokie, IL 60076 (US). HOCKERMAN, Susan, L. [US/US]; 5319 W. Hutchinson, Chicago, IL 60641 (US). HOWARD, Susan, C. [US/US]; 35 Worthy Court, Fenton, MO 63026 (US). KOLODZIEJ, Steve, A. [US/US]; 2448 Carjon Road, Ballwin, MO 63021 (US). LI, Hui [—/US]; 322 Jefferson Court, Vernon Hills, IL 60061 (US). MISCHKE, Deborah, A. [US/US]; 25 White River Lane, Defiance, MO 63341 (US). RICO, Joseph, G. [US/US]; 524 Wetherby Terrace Drive, Ballwin, MO 63021 (US). STEHLE, Nathan, W. [US/US]; 212D Seawind Drive, Ballwin, MO 63021 (US). TOLLEFSON, Michael, B. [US/US]; 219 Brougham Drive, O'Fallon, MO 63306 (US). VERNIER, William, F. [FR/US]; 1535 G. Oak Forest Spur Drive, St. Louis, MO 63146 (US). VILLAMIL, Clara, I. [US/US]; 813 Long Road, Glenview, IL 60025 (US). RAO, Shashidhar, N. [IN/US]; 736 Bellerive Manor Drive, St. Louis, MO 63141 (US). (74) Agents: WARNER, James, M.; G.D. Searle & Co., Corporate Patent Department, 5200 Old Orchard Road, Skokie, IL 60077 (US) et al. (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: AROMATIC SULFONE HYDROXAMIC ACID METALLOPROTEASE INHIBITOR (57) Abstract A treatment process is disclosed that comprises administering an effective amount of an aromatic sulfone hydroxamic acid that exhibits excellent inhibitory activity of one or more matrix metalloprotease (MMP) enzymes, such as MMP-2, MMP-9 and MMP-13, while exhibiting substantially less inhibition at least of MMP-1 to a host having a condition associated with pathological matrix metalloprotease activity. Also disclosed are metalloprotease inhibitor compounds having those selective activities, processes for manufacture of such compounds and pharmaceutical compositions using an inhibitor. <div style="text-align: center; font-size: 2em; font-weight: bold;">EV 311408173 US</div>		

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AROMATIC SULFONE HYDROXAMIC ACID
METALLOPROTEASE INHIBITOR

Description

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Technical Field

This invention is directed to proteinase (protease) inhibitors, and more particularly to the use of aromatic sulfone hydroxamic acid compounds that, *inter alia*, are selective inhibitors of matrix metalloproteinases in a process for treating conditions associated with pathological matrix metalloproteinase activity, the selective inhibitors themselves, compositions of proteinase inhibitors, intermediates for the syntheses of proteinase inhibitors, and processes for the preparation of proteinase inhibitors.

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Background of the Invention

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Connective tissue, extracellular matrix constituents and basement membranes are required components of all mammals. These components are the biological materials that provide rigidity, differentiation, attachments and, in some cases, elasticity to biological systems including human beings and other mammals. Connective tissues components include, for example, collagen, elastin, proteoglycans, fibronectin and laminin. These biochemicals makeup, or are components of structures, such as skin, bone, teeth, tendon, cartilage, basement membrane, blood vessels, cornea and vitreous humor.

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Under normal conditions, connective tissue turnover and/or repair processes are controlled and in equilibrium. The loss of this balance for whatever reason leads to a number of disease states.

5 Inhibition of the enzymes responsible loss of equilibrium provides a control mechanism for this tissue decomposition and, therefore, a treatment for these diseases.

Degradation of connective tissue or
10 connective tissue components is carried out by the action of proteinase enzymes released from resident tissue cells and/or invading inflammatory or tumor cells. A major class of enzymes involved in this function are the zinc metalloproteinases
15 (metalloproteases).

The metalloprotease enzymes are divided into classes with some members having several different names in common use. Examples are: collagenase I (MMP-1, fibroblast collagenase; EC
20 3.4.24.3); collagenase II (MMP-8, neutrophil collagenase; EC 3.4.24.34), collagenase III (MMP-13), stromelysin 1 (MMP-3; EC 3.4.24.17), stromelysin 2 (MMP-10; EC 3.4.24.22), proteoglycanase, matrilysin (MMP-7), gelatinase A (MMP-2, 72 kDa gelatinase,
25 basement membrane collagenase; EC 3.4.24.24), gelatinase B (MMP-9, 92 kDa gelatinase; EC 3.4.24.35), stromelysin 3 (MMP-11), metalloelastase (MMP-12, HME, human macrophage elastase) and membrane MMP (MMP-14). MMP is an abbreviation or acronym
30 representing the term Matrix Metalloprotease with the attached numerals providing differentiation between specific members of the MMP group.

The uncontrolled breakdown of connective tissue by metalloproteases is a feature of many pathological conditions. Examples include rheumatoid arthritis, osteoarthritis, septic arthritis; corneal, 5 epidermal or gastric ulceration; tumor metastasis, invasion or angiogenesis; periodontal disease; proteinuria; Alzheimers Disease; coronary thrombosis and bone disease. Defective injury repair processes also occur. This can produce improper wound healing 10 leading to weak repairs, adhesions and scarring. These latter defects can lead to disfigurement and/or permanent disabilities as with post-surgical adhesions.

Metalloproteases are also involved in the 15 biosynthesis of tumor necrosis factor (TNF), and inhibition of the production or action of TNF and related compounds is an important clinical disease treatment mechanism. TNF- α , for example, is a cytokine that at present is thought to be produced 20 initially as a 28 kD cell-associated molecule. It is released as an active, 17 kD form that can mediate a large number of deleterious effects *in vitro* and *in vivo*. For example, TNF can cause and/or contribute to the effects of inflammation, rheumatoid arthritis, 25 autoimmune disease, multiple sclerosis, graft rejection, fibrotic disease, cancer, infectious diseases, malaria, mycobacterial infection, meningitis, fever, psoriasis, cardiovascular/pulmonary effects such as post-ischemic reperfusion 30 injury, congestive heart failure, hemorrhage, coagulation, hyperoxic alveolar injury, radiation damage and acute phase responses like those seen with infections and sepsis and during shock such as septic

shock and hemodynamic shock. Chronic release of active TNF can cause cachexia and anorexia. TNF can be lethal, and TNF can help control the growth of tumor cells.

5 TNF- α convertase is a metalloprotease involved in the formation of soluble TNF- α . Inhibition of TNF- α convertase (TACE) inhibits production of active TNF- α . Compounds that inhibit both MMPs activity and TNF- α production have been
10 disclosed in WIPO International Publication Nos. WO 94/24140, WO 94/02466 and WO 97/20824. Compounds that inhibit MMPs such as collagenase, stromelysin and gelatinase have been shown to inhibit the release of TNF (Gearing et al. *Nature* 376, 555-557 (1994),
15 McGeehan et al., *Nature* 376, 558-561 (1994)). There remains a need for effective MMP inhibitors. There also remains a need for effective TNF- α convertase inhibiting agents.

 MMPs are involved in other biochemical
20 processes in mammals as well. Included is the control of ovulation, post-partum uterine involution, possibly implantation, cleavage of APP (β -Amyloid Precursor Protein) to the amyloid plaque and inactivation of α_1 -protease inhibitor (α_1 -PI).

25 Inhibition of these metalloproteases permits the control of fertility and the treatment or prevention of Alzheimers Disease. In addition, increasing and maintaining the levels of an endogenous or administered serine protease inhibitor drug or
30 biochemical such as α_1 -PI supports the treatment and prevention of diseases such as emphysema, pulmonary

diseases, inflammatory diseases and diseases of aging such as loss of skin or organ stretch and resiliency.

Inhibition of selected MMPs can also be desirable in other instances. Treatment of cancer and/or inhibition of metastasis and/or inhibition of angiogenesis are examples of approaches to the treatment of diseases wherein the selective inhibition of stromelysin, gelatinase A or B, or collagenase III appear to be the relatively most important enzyme or enzymes to inhibit especially when compared with collagenase I (MMP-1). A drug that does not inhibit collagenase I can have a superior therapeutic profile. Osteoarthritis, another prevalent disease wherein it is believed that cartilage degradation of inflamed joints is at least partially caused by MMP-13 released from cells such as stimulated chondrocytes, may be best treated by administration of drugs one of whose modes of action is inhibition of MMP-13. See, for example, Mitchell et al., *J. Clin. Invest.*, 97:761-768 (1996) and Reboul et al., *J. Clin. Invest.*, 97:2011-2019 (1996).

Inhibitors of metalloproteases are known. Examples include natural biochemicals such as tissue inhibitors of metalloproteinases (TIMPs), α_2 -macroglobulin and their analogs or derivatives. These endogenous inhibitors are high molecular weight protein molecules that form inactive complexes with metalloproteases. A number of smaller peptide-like compounds that inhibit metalloproteases have been described. Mercaptoamide peptidyl derivatives have shown ACE inhibition *in vitro* and *in vivo*. Angiotensin converting enzyme (ACE) aids in the

production of angiotensin II, a potent pressor substance in mammals and inhibition of this enzyme leads to the lowering of blood pressure.

Thiol group-containing amide or peptidyl
5 amide-based metalloprotease (MMP) inhibitors are known as is shown in, for example, WO95/12389, WO96/11209 and U.S. 4,595,700. Hydroxamate group-containing MMP inhibitors are disclosed in a number of published patent applications such as WO 95/29892,
10 WO 97/24117, WO 97/49679 and EP 0 780 386 that disclose carbon back-boned compounds, and WO 90/05719, WO 93/20047, WO 95/09841 and WO 96/06074 that disclose hydroxamates that have a peptidyl back-bones or peptidomimetic back-bones, as does the
15 article by Schwartz et al., *Progr. Med. Chem.*, 29:271-334(1992) and those of Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997) and Denis et al., *Invest. New Drugs*, 15(3): 175-185 (1997).

One possible problem associated with known
20 MMP inhibitors is that such compounds often exhibit the same or similar inhibitory effects against each of the MMP enzymes. For example, the peptidomimetic hydroxamate known as batimastat is reported to exhibit IC₅₀ values of about 1 to about 20 nanomolar
25 (nM) against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat, another peptidomimetic hydroxamate was reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum very similar to batimastat, except that marimastat
30 exhibited an IC₅₀ value against MMP-3 of 230 nM. Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997).

Meta analysis of data from Phase I/II studies using marimastat in patients with advanced, rapidly progressive, treatment-refractory solid tumor cancers (colorectal, pancreatic, ovarian, prostate) indicated a dose-related reduction in the rise of cancer-specific antigens used as surrogate markers for biological activity. Although marimastat exhibited some measure of efficacy via these markers, toxic side effects were noted. The most common drug-related toxicity of marimastat in those clinical trials was musculoskeletal pain and stiffness, often commencing in the small joints in the hands, spreading to the arms and shoulder. A short dosing holiday of 1-3 weeks followed by dosage reduction permits treatment to continue. Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997). It is thought that the lack of specificity of inhibitory effect among the MMPs may be the cause of that effect.

International application WO 98/38163, published on September 3, 1998 disclose a large group of hydroxamate inhibitors of MMPs and TACE. The compounds of WO 98/38163 contain one or two substituents adjacent to the hydroxamate functionality and a substituent that can be an aromatic sulfonyl group adjacent to those one or two substituents.

International application WO 98/37877, published on September 3, 1998 discloses compounds that contain a 5- to 7-membered heterocyclic ring adjacent to the hydroxamate functionality and can

contain an aromatic sulfonyl group adjacent to the heterocyclic ring.

Although many of the known MMP inhibitors such as batimastat, marimastat and the hydroxamates of WO 98/37877 and WO 98/38163 exhibit a broad spectrum of activity against MMPs, those compounds are not particularly selective in their inhibitory activity. This lack of selectivity may be the cause of the musculoskeletal pain and stiffness observed with their use. In addition, it can be therapeutically advantageous to utilize a medicament that is selective in its activity as compared to a generally active material so that treatment can be more closely tailored to the pathological condition presented by the host mammal. The disclosure that follows describes a process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity that utilizes a compound that selectively inhibits one or more MMPs, while exhibiting less activity against at least MMP-1.

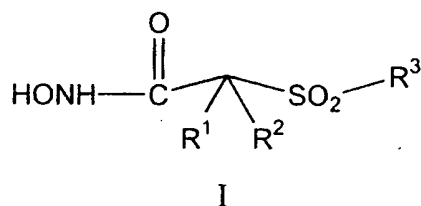
Summary of the Invention

The present invention is directed to a treatment process that comprises administering a contemplated aromatic sulfone hydroxamic acid metalloprotease inhibitor in an effective amount to a host mammal having a condition associated with pathological metalloprotease activity. A contemplated molecule, *inter alia*, exhibits excellent inhibitory activity of one or more matrix

metalloprotease (MMP) enzymes, such as MMP-2, MMP-9 and MMP-13, while exhibiting substantially less inhibition at least of MMP-1. By "substantially less" it is meant that a contemplated compound exhibits an IC_{50} value ratio against one or more of MMP-2, MMP-9 or MMP-13 as compared to its IC_{50} value against MMP-1, e.g., IC_{50} MMP-2: IC_{50} MMP-1, that is less than about 1:10, preferably less than about 1:100, and most preferably less than about 1:1000 in the *in vitro* inhibition assay utilized hereinafter. The invention also contemplates particular compounds that selectively inhibit the activity of one or more of MMP-2, MMP-9 and MMP-13, while exhibiting substantially less inhibition at least of MMP-1, as well as a composition containing such a MMP inhibitor as active ingredient. The invention further contemplates intermediates in the preparation of a contemplated aromatic sulfone hydroxamic acid molecule and a process for preparing an aromatic sulfone hydroxamic acid molecule.

Briefly, one embodiment of the present invention is directed to a treatment process that comprises administering a contemplated aromatic sulfone hydroxamic acid metalloprotease inhibitor that selectively inhibits matrix metalloprotease activity as above in an effective amount to a host mammal having a condition associated with pathological metalloprotease activity. The administered enzyme inhibitor corresponds in structure to formula (I), below, or a pharmaceutically acceptable salt thereof:

-10-



wherein

- 5 R^1 and R^2 are both hydrido or R^1 and R^2 together with the atoms to which they are bonded form a 5- to 8-membered ring containing one, two or three heteroatoms in the ring that are oxygen, sulfur or nitrogen.
- 10 R^3 in formula I is an optionally substituted aryl or optionally substituted heteroaryl radical. When R^3 is a substituted aryl or heteroaryl radical, a contemplated substituent is selected from the group consisting of an aryl, heteroaryl, aralkyl,
- 15 heteroaralkyl, aryloxy, arylthio, aralkoxy, heteroaralkoxy, aralkoxyalkyl, aryloxyalkyl, aralkanoylalkyl, arylcarbonylalkyl, aralkylaryl, aryloxyalkylaryl, aralkoxyaryl, arylazoaryl, arylhydrazinoaryl, alkylthioaryl, arylthioalkyl,
- 20 alkylthioaralkyl, aralkylthioalkyl, an aralkylthioaryl radical, the sulfoxide or sulfone of any of the thio substituents, and a fused ring structure comprising two or more 5- or 6-membered rings selected from the group consisting of aryl,
- 25 heteroaryl, carbocyclic and heterocyclic.

The substituent bonded to the aryl or heteroaryl radical of which the R^3 radical is comprised itself can be substituted with one or more substituents;

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i.e., the substituting substituent is optionally substituted. When that aryl or heteroaryl radical is substituted, and the substituting moiety (group, substituent, or radical) is itself substituted, the last-named substituent is independently selected from the group consisting of a cyano, perfluoroalkyl, trifluoromethoxy, trifluoromethylthio, haloalkyl, trifluoromethylalkyl, aralkoxycarbonyl, aryloxycarbonyl, hydroxy, halo, alkyl, alkoxy, nitro, thiol, hydroxycarbonyl, aryloxy, arylthio, aralkyl, aryl, arylcarbonylamino, heteroaryloxy, heteroarylthio, heteroaralkyl, cycloalkyl, heterocyclooxy, heterocyclothio, heterocycloamino, cycloalkyloxy, cycloalkylthio, heteroaralkoxy, heteroaralkylthio, aralkoxy, aralkylthio, aralkylamino, heterocyclo, heteroaryl, arylazo, hydroxycarbonylalkoxy, alkoxycarbonylalkoxy, alkanoyl, arylcarbonyl, aralkanoyl, alkanoyloxy, aralkanoyloxy, hydroxyalkyl, hydroxyalkoxy, alkylthio, alkoxyalkylthio, alkoxycarbonyl, aryloxyalkoxyaryl, arylthioalkylthioaryl, aryloxyalkylthioaryl, arylthioalkoxyaryl, hydroxycarbonylalkoxy, hydroxycarbonylalkylthio, alkoxycarbonylalkoxy, alkoxycarbonylalkylthio, amino, wherein the amino nitrogen is (i) unsubstituted, or (ii) substituted with one or two substituents that are independently selected from the group consisting of an alkyl, aryl, heteroaryl, aralkyl, cycloalkyl, aralkoxycarbonyl, alkoxycarbonyl, arylcarbonyl, aralkanoyl, heteroarylcarbonyl, heteroaralkanoyl and an alkanoyl group, or (iii) wherein the amino nitrogen and two substituents attached thereto

form a 5- to 8-membered heterocyclo or heteroaryl ring containing zero to two additional heteroatoms that are nitrogen, oxygen or sulfur and which ring itself is (a) unsubstituted or (b) substituted with one or two groups independently selected from the group consisting of an aryl, alkyl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, alkoxy, alkanoyl, cycloalkyl, heterocycloalkyl, alkoxy carbonyl, hydroxyalkyl, trifluoromethyl, benzofused heterocycloalkyl, hydroxyalkoxyalkyl, aralkoxy carbonyl, hydroxy carbonyl, aryloxy carbonyl, benzofused heterocycloalkoxy, benzofused cycloalkyl carbonyl, heterocycloalkyl carbonyl, and a cycloalkyl carbonyl group, carbonylamino

wherein the carbonylamino nitrogen is (i) unsubstituted, or (ii) is the reacted amine of an amino acid, or (iii) substituted with one or two radicals selected from the group consisting of an alkyl, hydroxyalkyl, hydroxyheteroaralkyl, cycloalkyl, aralkyl, trifluoromethylalkyl, heterocycloalkyl, benzofused heterocycloalkyl, benzofused heterocycloalkyl, benzofused cycloalkyl, and an N,N-dialkylsubstituted alkylamino-alkyl group, or (iv) the carboxamido nitrogen and two substituents bonded thereto together form a 5- to 8-membered heterocyclo, heteroaryl or benzofused heterocycloalkyl ring that is itself unsubstituted or substituted with one or two radicals independently selected from the group consisting of an alkyl, alkoxy carbonyl, nitro, heterocycloalkyl,

hydroxy, hydroxycarbonyl, aryl, aralkyl,
heteroaralkyl and an amino group,

wherein the amino nitrogen is

(i) unsubstituted, or (ii) substituted with

5 one or two substituents that are

independently selected from the group

consisting of alkyl, aryl, and heteroaryl,

or (iii) wherein the amino nitrogen and two
substituents attached thereto form a 5- to

10 8-membered heterocyclo or heteroaryl ring,

and an aminoalkyl group

wherein the aminoalkyl nitrogen is (i) unsubstituted,

or (ii) substituted with one or two substituents

independently selected from the group consisting of

15 an alkyl, aryl, aralkyl, cycloalkyl,

aralkoxycarbonyl, alkoxycarbonyl, and an alkanoyl

group, or (iii) wherein the aminoalkyl nitrogen and

two substituents attached thereto form a 5- to 8-

membered heterocyclo or heteroaryl ring.

20 In preferred practice, R^1 and R^2 together
with the atoms to which they are bonded form a
6-membered ring.

An R^3 radical preferably has a length that
is greater than that of a pentyl group [a $-(CH_2)_4CH_3$

25 chain] and more preferably greater than about that of

a hexyl group [a $-(CH_2)_5CH_3$ chain]. An R^3 radical

preferably has a length that is less than that of an

icosyl group [a $-(CH_2)_{19}CH_3$ chain], and more

preferably a length that is less than that of a

30 stearyl group [a $-(CH_2)_{17}CH_3$ chain]. A preferred R^3

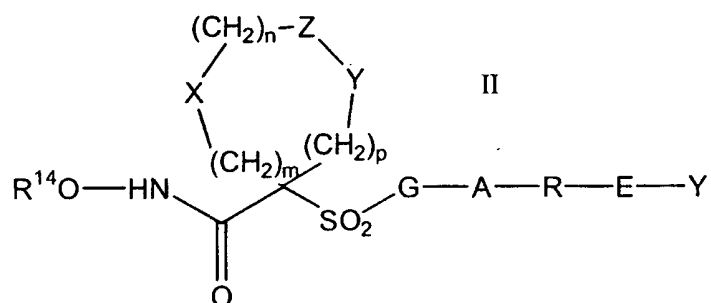
group contains two or more 5- or 6-membered rings. A

contemplated R^3 group, when rotated about an axis drawn through the SO_2 -bonded 1-position and the substituent-bonded 4-position of a 6-membered ring or the SO_2 -bonded 1-position and substituent-bonded 3-
5 or 4-position of a 5-membered ring, defines a three-dimensional volume whose widest dimension has the width in a direction transverse to that axis to rotation of about one furanyl ring to about two phenyl rings.

10 It is also preferred that a R^3 radical be a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring or at its own 3- or 4-position when a 5-membered ring with an optionally
15 substituted substituent selected from the group consisting of one other single-ringed aryl or heteroaryl group, a C_3 - C_{14} alkyl group, a N-piperidyl group, a N-piperazyl group, a phenoxy group, a thiophenoxy group, a 4-thiopyridyl group, a phenylazo
20 group and a benzamido group. The substituent of the 5- or 6-membered aryl or heteroaryl group can itself be substituted as discussed before.

A preferred compound for use in a contemplated process has a structure that corresponds to formula
25 II, below, or a pharmaceutically acceptable salt thereof:

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wherein

R^{14} is hydrido, a pharmaceutically

5 acceptable cation or $C(W)R^{15}$ where W is O or S and R^{15} is selected from the group consisting of an C_1 - C_6 -alkyl, aryl, C_1 - C_6 -alkoxy, heteroaryl- C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, aryloxy, ar- C_1 - C_6 -alkoxy, ar- C_1 - C_6 -alkyl, heteroaryl and amino C_1 - C_6 -alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of an C_1 - C_6 -alkyl, aryl, ar- C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, ar- C_1 - C_6 -alkoxycarbonyl, C_1 - C_6 -alkoxycarbonyl, and C_1 - C_6 -alkanoyl radical, or (iii) wherein the amino C_1 - C_6 -alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring;

20 m is zero, 1 or 2;

n is zero, 1 or 2;

p is zero, 1 or 2;

the sum of $m + n + p = 1, 2, 3$ or 4;

(a) one of X, Y and Z is selected from the

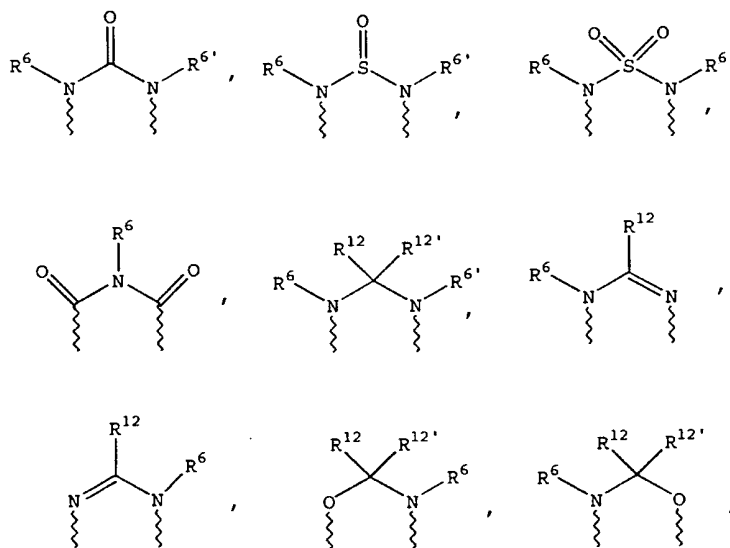
25 group consisting of $C(O)$, NR^6 , O, S, $S(O)$, $S(O)_2$ and

$\text{NS(O)}_2\text{R}^7$, and the remaining two of X, Y and Z are

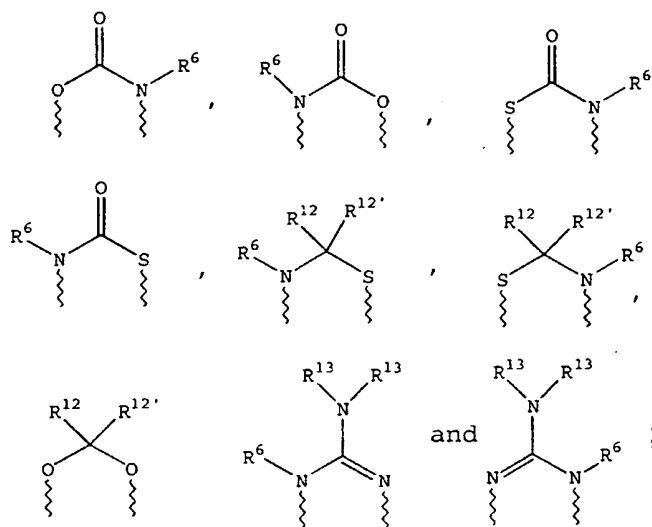
CR^8R^9 , and $\text{CR}^{10}\text{R}^{11}$, or

(b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting
 5 of $\text{NR}^6\text{C(O)}$, $\text{NR}^6\text{S(O)}$, $\text{NR}^6\text{S(O)}_2$, NR^6S , NR^6O , SS , NR^6NR^6
 and OC(O) , with the remaining one of X, Y and Z being
 CR^8R^9 , or

(c) n is zero and X, Y and Z together
 constitute a moiety selected from the group
 10 consisting of



-17-



wherein wavy lines are bonds to the atoms of the depicted ring;

- 5 R⁶ and R^{6'} are independently selected from the group consisting of hydrido, C₁-C₆-alkanoyl, C₆-aryl-C₁-C₆-alkyl, aroyl, bis(C₁-C₆-alkoxy-C₁-C₆-alkyl)-C₁-C₆-alkyl, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-perfluoroalkyl, C₁-C₆-trifluoromethylalkyl, C₁-C₆-perfluoroalkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₃-C₈-heterocycloalkyl, C₃-C₈-heterocycloalkylcarbonyl, C₆-aryl, C₅-C₆-heterocyclo, C₅-C₆-heteroaryl, C₃-C₈-cycloalkyl-C₁-C₆-alkyl, C₆-aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, heteroaryl-C₁-C₆-alkoxy-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, C₆-arylsulfonyl, C₁-C₆-alkylsulfonyl, C₅-C₆-heteroarylsulfonyl, carboxy-C₁-C₆-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₆-alkyl, aminocarbonyl, C₁-C₆-alkyliminocarbonyl, C₆-
- 10
- 15

aryliminocarbonyl, C₅-C₆-heterocycloiminocarbonyl,
C₆-arylthio-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl,
C₆-arylthio-C₃-C₆-alkenyl, C₁-C₄-alkylthio-C₃-C₆-
alkenyl, C₅-C₆-heteroaryl-C₁-C₆-alkyl, halo-C₁-C₆-
5 alkanoyl, hydroxy-C₁-C₆-alkanoyl, thiol-C₁-C₆-
alkanoyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₁-C₄-alkoxy-
C₁-C₄-alkyl, C₁-C₅-alkoxycarbonyl, aryloxycarbonyl,
NR⁸R⁹-C₁-C₅-alkylcarbonyl, hydroxy-C₁-C₅-alkyl, an
aminocarbonyl wherein the aminocarbonyl nitrogen is
10 (i) unsubstituted or (ii) substituted with one or two
radicals independently selected from the group
consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-
cycloalkyl and a C₁-C₆-alkanoyl group,
hydroxyaminocarbonyl, an aminosulfonyl group wherein
15 the aminosulfonyl nitrogen is (i) unsubstituted or
(ii) substituted with one or two radicals
independently selected from the group consisting of
C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a
C₁-C₆-alkanoyl group, an amino-C₁-C₆-alkylsulfonyl
20 group wherein the amino-C₁-C₆-alkylsulfonyl nitrogen
is (i) unsubstituted or (ii) substituted with one or
two radicals independently selected from the group
consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-
cycloalkyl and a C₁-C₆-alkanoyl group and an amino-
25 C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is
(i) unsubstituted or (ii) substituted with one or two
radicals independently selected from the group
consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-
cycloalkyl and a C₁-C₆-alkanoyl group;

R⁷ is selected from the group consisting of a arylalkyl, aryl, heteroaryl, heterocyclo, C₁-C₆-alkyl, C₃-C₆-alkynyl, C₃-C₆-alkenyl, C₁-C₆-carboxyalkyl and a C₁-C₆-hydroxyalkyl group;

- 5 R⁸ and R⁹ and R¹⁰ and R¹¹ are independently selected from the group consisting of a hydrido, hydroxy, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroar-C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aralkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹ and the carbon to which they are bonded form a carbonyl group, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹, or R⁸ and R¹⁰ together with the atoms to which they

are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or sulfur, with the proviso that only one of R⁸ and R⁹ or R¹⁰ and R¹¹ is hydroxy;

R¹² and R^{12'} are independently selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroaralkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl;

R¹³ is selected from the group consisting of a hydrido, benzyl, phenyl, C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl and a C₁-C₆-hydroxyalkyl group; and

G-A-R-E-Y is a substituent that preferably has a length greater than that of a pentyl group, and more preferably has a length greater than that of a hexyl group. The substituent G-A-R-E-Y preferably has a
5 length that is less than that of an icosyl group, and is more preferably less than that of a stearyl group. In this substituent:

G is an aryl or heteroaryl group;

A is selected from the group consisting of

- 10 (1) -O-;
(2) -S-;
(3) -NR¹⁷-;
(4) -CO-N(R¹⁷) or -N(R¹⁷)-CO-, wherein R¹⁷ is hydrogen, C₁-C₄-alkyl, or phenyl;
15 (5) -CO-O- or -O-CO-;
(6) -O-CO-O-;
(7) -HC=CH-;
(8) -NH-CO-NH-;
(9) -C≡C-;
20 (10) -NH-CO-O- or -O-CO-NH-;
(11) -N=N-;
(12) -NH-NH-; and
(13) -CS-N(R¹⁸)- or -N(R¹⁸)-CS-, wherein R¹⁸ is hydrogen C₁-C₄-alkyl, or
25 phenyl; or
(14) A is absent and G is bonded directly to R;

R is a moiety selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl,
30 cycloalkyl, heterocycloalkyl, aralkyl, heteroaralkyl,

heterocycloalkylalkyl, cycloalkylalkyl,
cycloalkoxyalkyl, heterocycloalkoxyalkyl,
aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl,
heteroarylthioalkyl, cycloalkylthioalkyl, and a
5 heterocycloalkylthioalkyl group wherein the aryl or
heteroaryl or cycloalkyl or heterocycloalkyl
substituent is (i) unsubstituted or (ii) substituted
with one or two radicals selected from the group
consisting of a halo, alkyl, perfluoroalkyl,
10 perfluoroalkoxy, perfluoroalkylthio,
trifluoromethylalkyl, amino, alkoxycarbonylalkyl,
alkoxy, C₁-C₂-alkylene-dioxy, hydroxycarbonylalkyl,
hydroxycarbonylalkylamino, nitro, hydroxy,
hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl
15 group, and R is other than alkyl or alkoxyalkyl when
A is -O- or -S-;

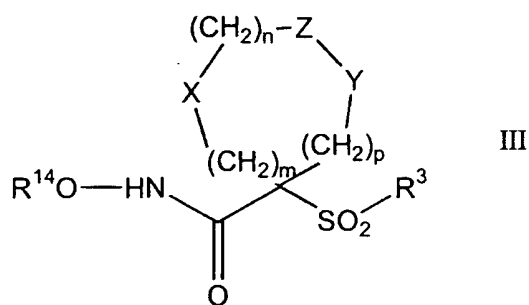
E is selected from the group consisting of

- (1) -CO(R¹⁹)- or -(R¹⁹)CO-, wherein R¹⁹ is
a heterocycloalkyl, or a cycloalkyl
20 group;
- (2) -CONH- or -HNCO-; and
- (3) -CO-;
- (4) -SO₂-R¹⁹- or -R¹⁹-SO₂-;
- (5) -SO₂-;
- 25 (6) -NH-SO₂- or -SO₂-NH-; or
- (7) E is absent and R is bonded directly
to Y; and

Y is absent or is selected from the group
consisting of a hydrido, alkyl, alkoxy, haloalkyl,
30 aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy,

aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl,
 perfluoroalkoxy, perfluoroalkylthio,
 trifluoromethylalkyl, alkenyl, heterocycloalkyl,
 cycloalkyl, trifluoromethyl, alkoxy, carbonyl, and a
 5 aminoalkyl group, wherein the aryl or heteroaryl or
 heterocycloalkyl group is (i) unsubstituted or (ii)
 substituted with one or two radicals independently
 selected from the group consisting of an alkanoyl,
 halo, nitro, aralkyl, aryl, alkoxy, and an amino
 10 group wherein the amino nitrogen is (i) unsubstituted
 or (ii) substituted with one or two groups
 independently selected from hydrido, alkyl, and an
 aralkyl group.

A particularly preferred compound for use
 15 in a contemplated process corresponds in structure to
 formula III, below, or a pharmaceutically acceptable
 salt thereof:



20

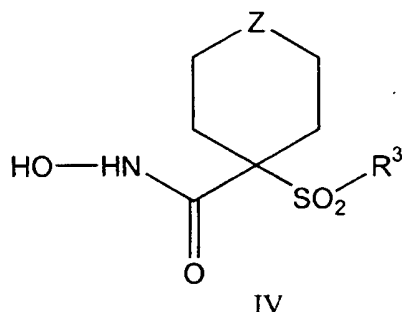
wherein

m, n, p, X, Z, Y and R¹⁴ are as defined above
 for formula II, and the R³ radical that is defined

below is a sub-set of the previously discussed G-A-R-E-Y substituents.

Thus, R³ is a radical that is comprised of a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring with a substituent selected from the group consisting of a thiophenoxy, 4-chlorophenoxy, 3-chlorophenoxy, 4-methoxyphenoxy, 3-benzodioxol-5-yloxy, 3,4-dimethylphenoxy, 4-fluorophenoxy, 4-fluorothiophenoxy, phenoxy, 4-trifluoromethoxy-phenoxy, 4-trifluoromethylphenoxy, 4-(trifluoromethylthio)-phenoxy, 4-(trifluoromethylthio)-thiophenoxy, 4-chloro-3-fluorophenoxy, 4-isopropoxyphenoxy, 4-isopropylphenoxy, (2-methyl-1,3-benzothiazol-5-yl)oxy, 4-(1H-imidazol-1-yl)phenoxy, 4-chloro-3-methylphenoxy, 3-methylphenoxy, 4-ethoxyphenoxy, 3,4-difluorophenoxy, 4-chloro-3-methylphenoxy, 4-fluoro-3-chlorophenoxy, 4-(1H-1,2,4-triazol-1-yl)phenoxy, 3,5-difluorophenoxy, 3,4-dichlorophenoxy, 4-cyclopentylphenoxy, 4-bromo-3-methylphenoxy, 4-bromophenoxy, 4-methylthiophenoxy, 4-phenylphenoxy, 4-benzylphenoxy, 6-quinolinyloxy, 4-amino-3-methylphenoxy, 3-methoxyphenoxy, 5,6,7,8-tetrahydro-2-naphthalenyloxy, 3-hydroxymethylphenoxy, N-piperidyl, N-piperazinyl and a 4-benzyloxyphenoxy group.

A more particularly preferred compound for use in a contemplated process has a structure that corresponds to formula IV, below, or a pharmaceutically acceptable salt thereof:



wherein R^3 is as defined above for formula I,
 5 more preferably as defined for formula II (wherein
 this R^3 group is the G-A-R-E-Y substituent), and more
 preferably still as defined for formula III, and

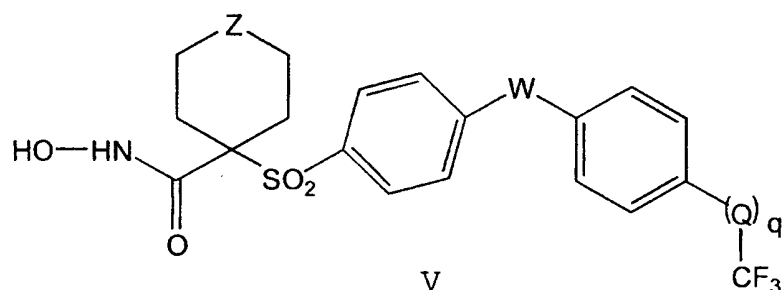
Z is selected group the group consisting of O,
 S, NR^6 , SO, SO_2 , and NSO_2R^7 ,

10 wherein R^6 is selected from the group consisting
 of hydrido, C_1 - C_5 -alkyl, C_1 - C_5 -alkanoyl, benzyl,
 benzoyl, C_3 - C_5 -alkynyl, C_3 - C_5 -alkenyl, C_1 - C_3 -alkoxy-
 C_1 - C_4 -alkyl, C_3 - C_6 -cycloalkyl, heteroaryl- C_1 - C_6 -
 alkyl, C_1 - C_5 -hydroxyalkyl, C_1 - C_5 -carboxyalkyl, C_1 - C_5 -
 15 alkoxy C_1 - C_5 -alkylcarbonyl, and NR^8R^9 - C_1 - C_5 -
 alkylcarbonyl or NR^8R^9 - C_1 - C_5 -alkyl wherein R^8 and R^9
 are independently hydrido, C_1 - C_5 -alkyl, C_1 - C_5 -
 alkoxy carbonyl or aryl- C_1 - C_5 -alkoxy carbonyl, or NR^8R^9
 together form a heterocyclic ring containing 5- to 8-
 20 atoms in the ring; and

R^7 is selected from the group consisting of an
 arylalkyl, aryl, heteroaryl, heterocyclo, C_1 - C_6 -

alkyl, C₃-C₆-alkynyl, C₃-C₆-alkenyl, C₁-C₆-carboxyalkyl and a C₁-C₆-hydroxyalkyl group.

A still more preferred group of compounds for use in a contemplated process correspond in structure to formula V, below, or a pharmaceutically acceptable salt thereof:



10 wherein

Z is as previously defined in formula IV;

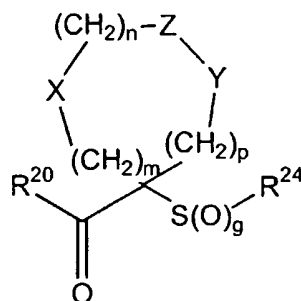
W and Q are independently oxygen (O), NR⁶ or sulfur (S), and R⁶ is as defined in formula IV; and

q is zero or one such that when q is zero, the trifluoromethyl group is bonded directly to the depicted phenyl ring.

The use of a compound of formulas I-V, or a pharmaceutically acceptable salt of one of those compounds is contemplated in a before-described process. In addition, the compounds of formulas II, III, IV and V, and their pharmaceutically acceptable salts are contemplated compounds of this invention.

The present invention also contemplates a precursor or intermediate compound that is useful in preparing a compound of formulas I-V. Such an

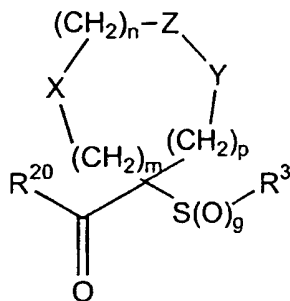
intermediate compound corresponds in structure to formula VI, below:



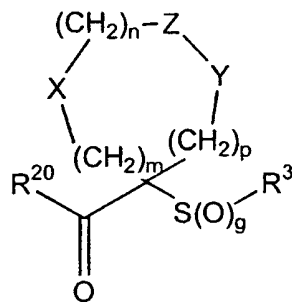
VI

5

wherein m, n, p, X, Z and Y are as defined above for formula II, g is zero, 1 or 2 and R²⁴ is R³ as defined in formulas I, III or IV, is the
 10 substituent G-A-R-E-Y of formula II (formula VIA) or is R^{3'}, an aryl or heteroaryl group that is substituted with a coupling substituent reactive for coupling with another moiety (formula VIB), such as a nucleophilically displaceable leaving group, D.



VIA



VIB

15

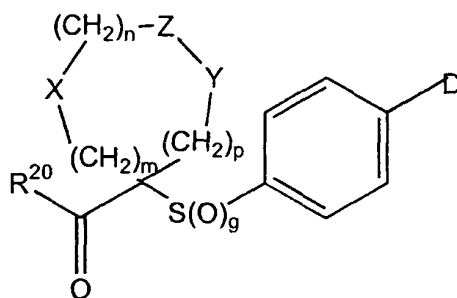
Exemplary nucleophilically displaceable leaving groups, D, include a halo (fluoro, chloro, bromo, or iodo) nitro, azido, phenylsulfoxido,

aryloxy, C₁-C₆-alkoxy, a C₁-C₆-alkylsulfonate or arylsulfonate group and a trisubstituted ammonium group in which the three substituents are independently aryl, ar-C₁-C₆-alkyl or C₁-C₆-alkyl.

- 5 R²⁰ is (a) -O-R²¹, where R²¹ is selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl group and a pharmaceutically acceptable cation, (b) -NH-O-R²² wherein R²² is a selectively removable protecting group such as a 2-
10 tetrahydropyranyl, benzyl, p-methoxybenzyl (MOZ), carbonyl-C₁-C₆-alkoxy, trisubstituted silyl group or o-nitrophenyl group, peptide synthesis resin and the like, wherein the trisubstituted silyl group is substituted with C₁-C₆-alkyl, aryl, or ar-C₁-C₆-alkyl
15 or a mixture thereof, (c) -NH-O-R¹⁴, where R¹⁴ is hydrido, a pharmaceutically acceptable cation or C(W)R²⁵ where W is O (oxo) or S (thioxo) and R²⁵ is selected from the group consisting of an C₁-C₆-alkyl, aryl, C₁-C₆-alkoxy, heteroaryl-C₁-C₆-alkyl, C₃-C₈-
20 cycloalkyl-C₁-C₆-alkyl, aryloxy, ar-C₁-C₆-alkoxy, ar-C₁-C₆-alkyl, heteroaryl and amino C₁-C₆-alkyl group wherein the amino C₁-C₆-alkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group
25 consisting of an C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl-C₁-C₆-alkyl, ar-C₁-C₆-alkoxycarbonyl, C₁-C₆-alkoxycarbonyl, and C₁-C₆-alkanoyl radical, or (iii) wherein the amino C₁-C₆-alkyl nitrogen and two substituents attached thereto

form a 5- to 8-membered heterocyclo or heteroaryl ring, or (d) $-NR^{26}R^{27}$, where R^{26} and R^{27} are independently selected from the group consisting of a hydrido, C_1 - C_6 -alkyl, amino C_1 - C_6 -alkyl, hydroxy C_1 - C_6 -alkyl, aryl, ar- C_1 - C_6 -alkyl group, or R^{26} and R^{27} together with the depicted nitrogen atom form a 5- to 8-membered ring containing zero or one additional heteroatom that is oxygen, nitrogen or sulfur.

A particularly preferred precursor intermediate to an intermediate compound of formula VI is an intermediate compound of formula VII



VII

wherein m , n , p , g , X , Z , Y , D and R^{20} are as defined above for formula VI.

Among the several benefits and advantages of the present invention are the provision of compounds and compositions effective as inhibitors of matrix metalloproteinase activity, the provision of such compounds and compositions that are effective for the inhibition of metalloproteinases implicated in diseases and disorders involving uncontrolled breakdown of connective tissue.

More particularly, a benefit of this invention is the provision of a compound and composition effective for selectively inhibiting certain metalloproteinases, such as one or more of

5 MMP-2, MMP-9 and MMP-13, associated with pathological conditions such as, for example, rheumatoid arthritis, osteoarthritis, septic arthritis, corneal, epidermal or gastric ulceration, tumor metastasis, invasion or angiogenesis, periodontal disease,

10 proteinuria, Alzheimer's Disease, coronary thrombosis and bone disease.

An advantage of the invention is the provision of compounds, compositions and methods effective for treating such pathological conditions

15 by selective inhibition of a metalloproteinase such as MMP-2, MMP-9 or MMP-13 associated with such conditions with minimal side effects resulting from inhibition of other metalloproteinases, such as MMP-1, whose activity is necessary or desirable for

20 normal body function.

Yet another advantage of the invention is the provision of a process for preparing such compounds.

Another benefit is the provision of a

25 method for treating a pathological condition associated with abnormal matrix metalloproteinase activity.

A further advantage of the invention is the provision of a process for preparing such

30 compositions.

Still further benefits and advantages of the invention will be apparent to the skilled worker from the disclosure that follows.

Detailed Description of the Invention

In accordance with the present invention, it has been discovered that certain aromatic sulfone hydroxamic acids (hydroxamates) are effective for inhibition of matrix metalloproteinases ("MMPs") believed to be associated with uncontrolled or otherwise pathological breakdown of connective tissue. In particular, it has been found that these certain aromatic sulfone hydroxamates are effective for inhibition of one or more enzymes such as MMP-2, MMP-9 and MMP-13, which can be particularly destructive to tissue if present or generated in abnormal quantities or concentrations, and thus exhibit a pathological activity. Included in that pathological activity is the assistance of tumors and tumor cells in the process of penetrating basement membrane, and developing a new or improved blood supply; i.e., angiogenesis.

Moreover, it has been discovered that these aromatic sulfone hydroxamates are selective in the inhibition of one or more of MMP-2, MMP-9 and MMP-13 without excessive inhibition of other collagenases essential to normal bodily function such as tissue turnover and repair. More particularly, it has been found that a contemplated aromatic sulfone hydroxamate of the invention, or a pharmaceutically acceptable salt thereof, is particularly active in inhibiting of one or more of MMP-2, MMP-9 and MMP-13 in an *in vitro* assay that is predictive of *in vivo* activity. In addition, while being selective for one or more of MMP-2, MMP-9 and MMP-13, a contemplated

aromatic sulfone hydroxamate, or its salt, has a limited or minimal *in vitro* inhibitory effect on MMP-1.

There is thus a substantial difference in the activity of a compound used in a contemplated process toward one or more of MMP-2, MMP-9 and MMP-13 and MMP-1. This substantial difference is assayed using the *in vitro* inhibition assay discussed in the examples. A substantial difference in activity corresponds to a compound exhibiting an IC₅₀ value against one or more of MMP-2, MMP-9 and MMP-13 that is about 0.1 times that of the compound against MMP-1, and more preferably 0.01 times that against MMP-1 and most preferably 0.001 times that against MMP-1, or more. Indeed, some compounds exhibit selectivity differences measured by IC₅₀ values that exceed the bounds of the assay at the number 100,000-fold. These selectivities are illustrated in the Inhibition Tables hereinafter.

Put differently, a contemplated compound can inhibit the activity of MMP-2 compared to MMP-9 or MMP-13 and MMP-1. Similarly, a contemplated compound can inhibit the activity of MMP-13 and MMP-2, while exhibiting less inhibition against MMP-1 and MMP-9. In addition, a contemplated compound can inhibit the activity of a MMP enzyme, while having less of an effect on tumor necrosis factor release.

The advantages of the selectivity of a contemplated compound can be appreciated, without wishing to be bound by theory, by considering the therapeutic uses the compounds. For example, inhibition of MMP-1 is suggested to be undesirable

due to its role as a housekeeping enzyme, helping to maintain normal connective tissue turnover and repair. Inhibition of MMP-1 can lead to toxicities or side effects such as joint or connective
5 tissue deterioration and pain. On the other hand, MMP-13 has been suggested to be intimately involved in the destruction of joint components in diseases such as osteoarthritis. Thus, potent and selective inhibition of MMP-13 compared with inhibition MMP-1
10 is highly desirable because a MMP-13 inhibitor can have a positive effect on disease progression in a patient in addition to having an anti-inflammatory effect.

Inhibition of MMP-2 and MMP-9 can be desirable
15 for inhibition of tumor growth, metastasis, invasion and/or angiogenesis. A profile of selective inhibition of MMP-2 and MMP-9 relative to MMP-1 can provide a therapeutic advantage.

Yet another advantage of a contemplated compound
20 is the selectivity with respect to tumor necrosis factor release and/or tumor necrosis factor receptor release that provides the physician with another factor to help select the best drug for a particular patient. While not wishing to be bound by theory, it
25 is believed that there are several factors to this type of selectivity to be considered.

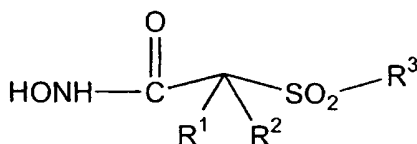
The first is that presence of tumor necrosis factor can be desirable for the control of cancer in the organism, so long as TNF is not present in a
30 toxic excess. Thus, uncontrolled inhibition of release of TNF can be counterproductive and actually can be considered an adverse side effect even in cancer patients. In addition, selectivity with

respect to inhibition of the release of the tumor necrosis factor receptor can also be desirable. The presence of that receptor can be desirable for maintaining a controlled tumor necrosis level in the mammal by binding excess TNF.

A contemplated selective MMP inhibitor compound useful in a contemplated process can be administered to by various routes and provide adequate therapeutic blood levels of enzymatically active inhibitor. A compound can be administered, for example, by the oral (IG, PO) or intravenous (IV) routes. Oral administration is advantageous if the patient is ambulatory, not hospitalized, physically able and sufficiently responsible to take drug at the required intervals. This is true even if the person is being treated with more than one drug for one or more diseases. On the other hand, IV drug administration is an advantage in a hospital setting wherein the dose and thus the blood levels can well controlled. A contemplated inhibitor can also be formulated for IM administration if desired. This route of administration can be desirable for the administration of prodrugs or regular drug delivery to patients that are either physically weak or have a poor compliance record or require constant drug blood levels.

Thus, in one embodiment, the present invention is directed to a treatment process that comprises administering a contemplated aromatic sulfone hydroxamic acid metalloprotease inhibitor, or a pharmaceutically acceptable salt thereof, in an effective amount to a host mammal having a condition

associated with pathological matrix metalloprotease activity. A contemplated aromatic sulfone hydroxamate inhibitor compound useful in such a process inhibits the activity of one or more of MMP-2, MMP-9 and MMP-13, and exhibits substantially less inhibitory activity against at least MMP-1 in the *in vitro* assay noted above and discussed in detail hereinbelow. An aromatic sulfone hydroxamate inhibitor compound for use in a contemplated process corresponds in structure to formula I, below:



I

wherein

In one embodiment, R^1 and R^2 are both hydrido. In another embodiment, R^1 and R^2 together with the atoms to which they are bonded form a 5- to 8-membered ring containing one, two or three heteroatoms in the ring that are oxygen, sulfur or nitrogen.

It is preferred that R^1 and R^2 together with the atoms to which they are bonded form a five- to eight-membered ring that contains one or two heteroatoms in the ring, although R^1 and R^2 together with the atoms to which they are bonded form a 5- to 8-membered ring containing one, two or three heteroatoms. The heterocyclic ring can itself also be substituted with up to six C_1 - C_6 -alkyl groups or groups that comprise

a another 5- to 8-membered carbocyclic or heterocyclic ring, an amino group, or contain one or two oxo (carbonyl) groups.

R^3 in formula I is an optionally substituted
5 aryl or optionally substituted heteroaryl radical.
That R^3 radical is selected from the group consisting of an aryl, heteroaryl, aralkyl, heteroaralkyl, aralkoxy, heteroaralkoxy, aralkoxyalkyl, aryloxyalkyl, aralkanoylalkyl, arylcarbonylalkyl,
10 aralkylaryl, aryloxyalkylaryl, aralkoxyaryl, arylazoaryl, arylhydrazinoaryl, alkylthioaryl, arylthioalkyl, alkylthioaralkyl, aralkylthioalkyl, an aralkylthioaryl radical, the sulfoxide or sulfone of any of the thio substituents, and a fused ring
15 structure comprising two or more 5- or 6-membered rings selected from the group consisting of aryl, heteroaryl, carbocyclic and heterocyclic.

The substituent of which R^3 is comprised itself is unsubstituted or substituted with one or more
20 substituents independently selected from the group consisting of a cyano, perfluoroalkyl, trifluoromethylalkyl, hydroxy, halo, alkyl, alkoxy, nitro, thiol, hydroxycarbonyl, aryloxy, arylthio, aralkyl, aryl, heteroaryloxy, heteroarylthio,
25 heteroaralkyl, cycloalkyl, heterocyclooxy, heterocyclothio, heterocycloamino, cycloalkyloxy, cycloalkylthio, heteroaralkoxy, heteroaralkylthio, aralkoxy, aralkylthio, aralkylamino, heterocyclo, heteroaryl, arylazo, hydroxycarbonylalkoxy,
30 alkoxycarbonylalkoxy, alkanoyl, arylcarbonyl, aralkanoyl, alkanoyloxy, aralkanoyloxy, hydroxyalkyl, hydroxyalkoxy, alkylthio, alkoxyalkylthio,

alkoxycarbonyl, aryloxyalkoxyaryl,
arylthioalkylthioaryl, aryloxyalkylthioaryl,
arylthioalkoxyaryl, hydroxycarbonylalkoxy,
hydroxycarbonylalkylthio, alkoxycarbonylalkoxy,
5 alkoxycarbonylalkylthio, amino,
wherein the amino nitrogen is (i) unsubstituted,
or (ii) substituted with one or two substituents
that are independently selected from the group
consisting of an alkyl, aryl, heteroaryl,
10 aralkyl, cycloalkyl, aralkoxycarbonyl,
alkoxycarbonyl, arylcarbonyl, aralkanoyl,
heteroarylcarbonyl, heteroaralkanoyl and an
alkanoyl group, or (iii) wherein the amino
nitrogen and two substituents attached thereto
15 form a 5- to 8-membered heterocyclo or
heteroaryl ring containing zero to two
additional heteroatoms that are nitrogen, oxygen
or sulfur and which ring itself is (a)
unsubstituted or (b) substituted with one or two
20 groups independently selected from the group
consisting of an aryl, alkyl, heteroaryl,
aralkyl, heteroaralkyl, hydroxy, alkoxy,
alkanoyl, cycloalkyl, heterocycloalkyl,
alkoxycarbonyl, hydroxyalkyl, trifluoromethyl,
25 benzofused heterocycloalkyl, hydroxyalkoxyalkyl,
aralkoxycarbonyl, hydroxycarbonyl,
aryloxycarbonyl, benzofused heterocycloalkoxy,
benzofused cycloalkylcarbonyl, heterocyclo-
alkylcarbonyl, and a cycloalkylcarbonyl group,
30 carbonylamino
wherein the carboxamido nitrogen is (i)
unsubstituted, or (ii) is the reacted amine of
an amino acid, or (iii) substituted with one or

two radicals selected from the group consisting of an alkyl, hydroxyalkyl, hydroxyheteroaralkyl, cycloalkyl, aralkyl, trifluoromethylalkyl, heterocycloalkyl, benzofused heterocycloalkyl, benzofused heterocycloalkyl, benzofused cycloalkyl, and an N,N-dialkylsubstituted alkylamino-alkyl group, or (iv) the carboxamido nitrogen and two substituents bonded thereto together form a 5- to 8-membered heterocyclo, heteroaryl or benzofused heterocycloalkyl ring that is itself unsubstituted or substituted with one or two radicals independently selected from the group consisting of an alkyl, alkoxy carbonyl, nitro, heterocycloalkyl, hydroxy, hydroxycarbonyl, aryl, aralkyl, heteroaralkyl and an amino group, wherein the amino nitrogen is (i) unsubstituted, or (ii) substituted with one or two substituents that are independently selected from the group consisting of alkyl, aryl, and heteroaryl, or (iii) wherein the amino nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring, and an aminoalkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted, or (ii) substituted with one or two substituents independently selected from the group consisting of an alkyl, aryl, aralkyl, cycloalkyl, aralkoxycarbonyl, alkoxy carbonyl, and an alkanoyl group, or (iii) wherein the aminoalkyl nitrogen and two substituents attached thereto form a 5- to 8-

membered heterocyclo or heteroaryl ring. A compound of formula I can also be used in the form of a pharmaceutically acceptable salt.

The R^3 radical has a length that is greater than
5 that of a pentyl group [a $-(CH_2)_4CH_3$ chain], and is more preferably greater than about the length of a hexyl group [a $-(CH_2)_5CH_3$ chain]. A R^3 group has a length that is less than that of an icosyl group [eicosyl; a $-(CH_2)_{19}CH_3$ chain], and more preferably,
10 a length that is less than that of a stearyl group [a $-(CH_2)_{17}CH_3$ chain]. When rotated about an axis drawn through the SO_2 -bonded 1-position and the substituent-bonded 4-position of a 6-membered ring or the SO_2 -bonded 1-position and substituent-bonded 3-
15 or 4-position of a 5-membered ring, a contemplated R^3 radical defines a three-dimensional volume whose widest dimension has the width of about one furanyl ring to about two phenyl rings in a direction transverse to that axis to rotation.

20 Where the SO_2 -linked R^3 radical is 4-phenoxyphenyl for purposes of illustration, a contemplated compound can be viewed as a phenoxyphenylsulfone derivative of the desired 5- to 8-membered ring N-hydroxycarboxamide. Exemplary
25 compounds can therefore be named:

N-hydroxy-1-methyl-[4-(phenoxyphenylsulfonyl)]-4-piperidinecarboxamide,

N-hydroxy-[4-(phenoxyphenylsulfonyl)]tetrahydro-2H-pyran-4-carboxamide,

30 N-hydroxy-1-methyl-[2,6-dioxo-4-(phenoxyphenylsulfonyl)]-4-piperidinecarboxamide,

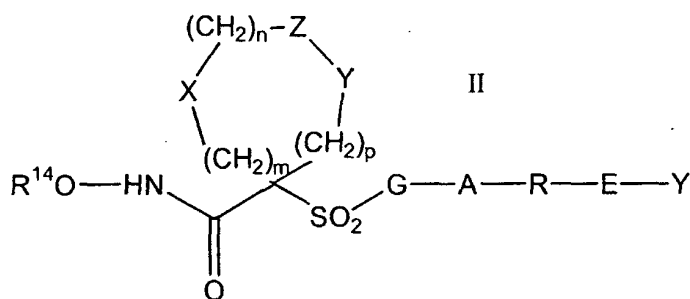
- N-hydroxy-2,2-dimethyl-[5-(phenoxyphenyl-sulfonyl)]-1,3-dioxane-5-carboxamide,
- N-hydroxy-1,2-dimethyl-6-oxo-[4-(phenoxyphenyl-sulfonyl)]-4-piperidinecarboxamide,
- 5 N-hydroxy-2,2,6,6-tetramethyl-[4-(phenoxyphenyl-sulfonyl)]-4-piperidinecarboxamide,
- N-hydroxy-1,3-dimethyl-[5-(phenoxyphenyl-sulfonyl)]-hexahydro-5-pyrimidinecarboxamide,
- 2-amino-N-hydroxy-[5-(phenoxyphenylsulfonyl)]-
- 10 1,4,5,6-tetrahydro-5-pyrimidinecarboxamide,
- N-hydroxy-1,1-dioxo-[4-(phenoxyphenylsulfonyl)]-
- 1(λ6),2,6-thiadiazinane-4-carboxamide,
- N-hydroxy-2-oxo-[5-(phenoxyphenylsulfonyl)]-
- hexahydro-5-pyrimidinecarboxamide,
- 15 N-hydroxy-[2-(phenoxyphenylsulfonyl)]tetrahydro-
- 2-furancarboxamide,
- N-hydroxy-1-methyl-[2-(phenoxyphenylsulfonyl)]-
- 2-pyrrolidinecarboxamide,
- N-hydroxy-2-methyl-[4-(phenoxyphenylsulfonyl)]-
- 20 4-piperidinecarboxamide,
- N-hydroxy-[3-(phenoxyphenylsulfonyl)]-8-
- azabicyclo[3.2.1]octane-3-carboxamide,
- N-hydroxy-1,1-dioxo-[4-(phenoxyphenylsulfonyl)]-
- hexahydro-1(λ6)-thiopyran-4-carboxamide,
- 25 N-hydroxy-[3-(phenoxyphenylsulfonyl)]tetrahydro-
- 3-furancarboxamide,
- N-hydroxy-[3-(phenoxyphenylsulfonyl)]-3-
- pyrrolidinecarboxamide,
- N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-
- 30 (2-propynyl)-4-piperidinecarboxamide,
- monohydrochloride,

- N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, monomethanesulfonate,
- tetrahydro-N-hydroxy-4-[[4-[4-
5 [(trifluoromethyl)phenoxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide,
- N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide, hydrochloride,
- 10 N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide, dihydrochloride,
- N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]-sulfonyl]-4-
15 piperidinecarboxamide, dihydrochloride,
- hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]-sulfonyl]-4-piperidinecarboxamide, dihydrochloride,
- N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-
20 piperidinecarboxamide, monohydrochloride,
- N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride,
- 25 N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-[(trifluoromethyl)thio]phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride,
- 1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidine-
30 carboxamide, monohydrochloride, and the like.

Several exemplary R¹ and R² groups that together form a contemplated heterocyclic ring are shown in

the Tables that follow hereinafter, as well as in the descriptions of those 5- to 8-membered rings and the specific Examples, as are several contemplated aromatic sulfone hydroxamic acid compounds.

- 5 In more preferred practice, R^1 and R^2 of formula I together with the atom to which they are bonded form a 5- to 8-membered ring that contains one, two or three heteroatoms. Most preferably, that ring is a 6-membered ring that contains one heteroatom
- 10 located at the 4-position relative to the position at which the SO_2 group is bonded. Other preferred compounds for use in a contemplated process correspond in structure to one or more of formulas II, III, IV or V, which are discussed hereinafter.
- 15 In one embodiment, a preferred compound used in a contemplated process has a structure that corresponds to formula II, below:



20

wherein

- R^{14} is hydrido, a pharmaceutically acceptable cation or $C(W)R^{15}$ where W is O or S and R^{15} is selected from the group consisting of an C_1 -
- 25 C_6 -alkyl, aryl, C_1 - C_6 -alkoxy, heteroaryl- C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, aryloxy, ar- C_1 - C_6 -

alkoxy, ar-C₁-C₆-alkyl, heteroaryl and amino C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group
5 consisting of an C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl-C₁-C₆-alkyl, ar-C₁-C₆-alkoxycarbonyl, C₁-C₆-alkoxycarbonyl, and C₁-C₆-alkanoyl radical, or (iii) wherein the amino C₁-C₆-alkyl nitrogen and two substituents attached thereto
10 form a 5- to 8-membered heterocyclo or heteroaryl ring;

m is zero, 1 or 2;

n is zero, 1 or 2;

p is zero, 1 or 2;

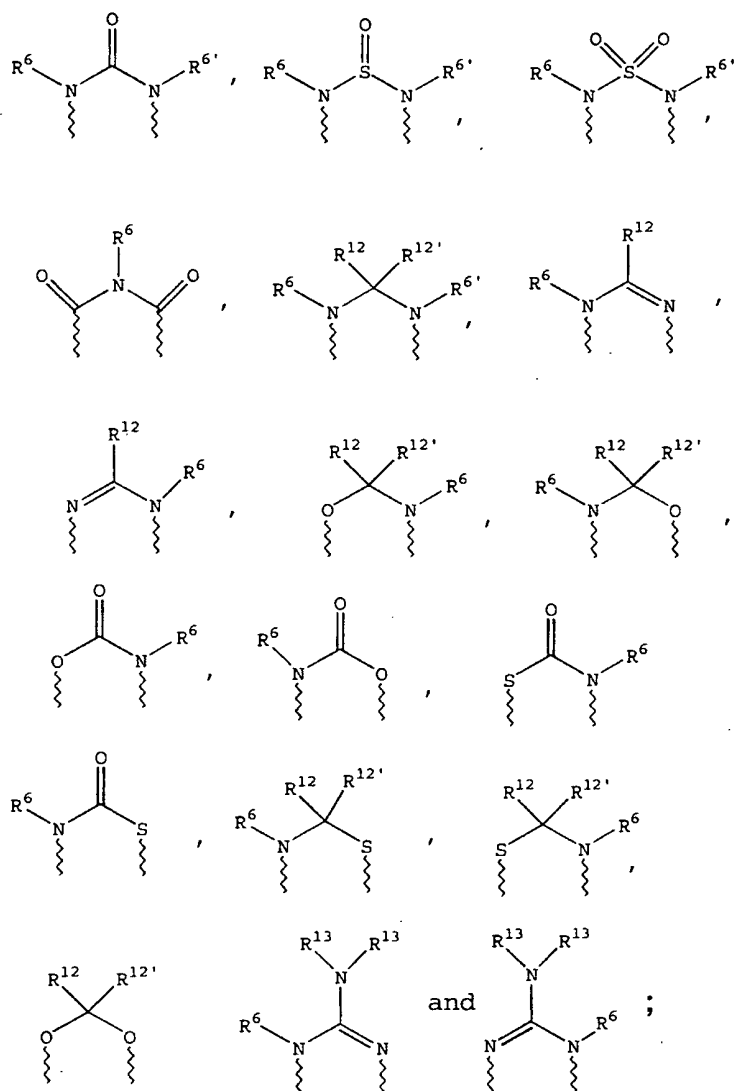
15 the sum of m + n + p = 1, 2, 3 or 4;

(a) one of X, Y and Z is selected from the group consisting of C(O), NR⁶, O, S, S(O), S(O)₂ and NS(O)₂R⁷, and the remaining two of X, Y and Z are CR⁸R⁹, and CR¹⁰R¹¹, or

20 (b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting of NR⁶C(O), NR⁶S(O), NR⁶S(O)₂, NR⁶S, NR⁶O, SS, NR⁶NR⁶ and OC(O), with the remaining one of X, Y and Z being CR⁸R⁹, or

25 (c) n is zero and X, Y and Z together constitute a moiety selected from the group consisting of

- 44 -



wherein wavy lines are bonds to the atoms of the
 5 depicted ring;

R⁶ and R^{6'} are independently selected from the
 group consisting of hydrido, C₁-C₆-alkanoyl, C₆-aryl-
 C₁-C₆-alkyl, aroyl, bis(C₁-C₆-alkoxy-C₁-C₆-alkyl)-C₁-
 C₆-alkyl, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-
 10 perfluoroalkyl, C₁-C₆-trifluoromethylalkyl, C₁-C₆-
 perfluoroalkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-

alkyl, C₃-C₆-cycloalkyl, C₃-C₈-heterocycloalkyl, C₃-C₈-heterocycloalkylcarbonyl, C₆-aryl, C₅-C₆-heterocyclo, C₅-C₆-heteroaryl, C₃-C₈-cycloalkyl-C₁-C₆-alkyl, C₆-aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, heteroaryl-C₁-C₆-alkoxy-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, C₆-arylsulfonyl, C₁-C₆-alkylsulfonyl, C₅-C₆-heteroarylsulfonyl, carboxy-C₁-C₆-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₆-alkyl, aminocarbonyl, C₁-C₆-alkyliminocarbonyl, C₆-aryliminocarbonyl, C₅-C₆-heterocycloiminocarbonyl, C₆-arylthio-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, C₆-arylthio-C₃-C₆-alkenyl, C₁-C₄-alkylthio-C₃-C₆-alkenyl, C₅-C₆-heteroaryl-C₁-C₆-alkyl, halo-C₁-C₆-alkanoyl, hydroxy-C₁-C₆-alkanoyl, thiol-C₁-C₆-alkanoyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₅-alkoxycarbonyl, aryloxycarbonyl, NR⁸R⁹-C₁-C₅-alkylcarbonyl, hydroxy-C₁-C₅-alkyl, an aminocarbonyl wherein the aminocarbonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group, hydroxyaminocarbonyl, an aminosulfonyl group wherein the aminosulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group, an amino-C₁-C₆-alkylsulfonyl

group wherein the amino-C₁-C₆-alkylsulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-
5 cycloalkyl and a C₁-C₆-alkanoyl group and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-
10 cycloalkyl and a C₁-C₆-alkanoyl group;

R⁷ is selected from the group consisting of a benzyl, phenyl, C₁-C₆-alkyl, C₃-C₆-alkynyl, C₃-C₆-alkenyl and a C₁-C₆-hydroxyalkyl group;

R⁸ and R⁹ and R¹⁰ and R¹¹ are independently
15 selected from the group consisting of a hydrido, hydroxy, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroar-C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl cycloalkyl, cycloalkyl-C₁-C₆-alkyl,
20 heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aralkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-
25 alkyl, heteroaryloxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-

alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹ and the carbon to which they are bonded form a carbonyl group, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹, or R⁸ and R¹⁰ together with the atoms to which they are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or sulfur, with the proviso that only one of R⁸ and R⁹ or R¹⁰ and R¹¹ is hydroxy;

R¹² and R^{12'} are independently selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroaralkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-

C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently
5 selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl;

R¹³ is selected from the group consisting of a hydrido, benzyl, phenyl, C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl and a C₁-C₆-hydroxyalkyl group; and

10 G-A-R-E-Y is a substituent that preferably has a length greater than that of a pentyl group, and more preferably has a length greater than that of a hexyl group. The substituent G-A-R-E-Y preferably has a length that is less than that of an icosyl group, and
15 is more preferably less than that of a stearyl group. In this substituent:

G is an aryl or heteroaryl group;

A is selected from the group consisting of

- 20 (1) -O-;
(2) -S-;
(3) -NR¹⁷-;
(4) -CO-N(R¹⁷) or -N(R¹⁷)-CO-, wherein R¹⁷ is hydrogen, C₁-C₄-alkyl, or phenyl;
(5) -CO-O- or -O-CO-;
25 (6) -O-CO-O-;
(7) -HC=CH-;
(8) -NH-CO-NH-;
(9) -C≡C-;
(10) -NH-CO-O- or -O-CO-NH-;

(11) -N=N-;

(12) -NH-NH-; and

(13) -CS-N(R¹⁸)- or -N(R¹⁸)-CS-, wherein

R¹⁸ is hydrogen C₁-C₄-alkyl, or

5 phenyl; or

(14) A is absent and G is bonded directly
to R;

R is a moiety selected from the group consisting
of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl,
10 heterocycloalkyl, aralkyl, heteroaralkyl,
heterocycloalkylalkyl, cycloalkylalkyl,
cycloalkoxyalkyl, heterocycloalkoxyalkyl,
aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl,
heteroarylthioalkyl, cycloalkylthioalkyl, and a
15 heterocycloalkylthioalkyl group wherein the aryl or
heteroaryl or cycloalkyl or heterocycloalkyl
substituent is (i) unsubstituted or (ii) substituted
with one or two radicals selected from the group
consisting of a halo, alkyl, perfluoroalkyl,
20 perfluoroalkoxy, perfluoroalkylthio,
trifluoromethylalkyl, amino, alkoxycarbonylalkyl,
alkoxy, C₁-C₂-alkylene-dioxy, hydroxycarbonylalkyl,
hydroxycarbonylalkylamino, nitro, hydroxy,
hydroxyalkyl, alkanoylamino, and a alkoxycarbonyl
25 group, and R is other than alkyl or alkoxyalkyl when
A is -O- or -S-;

E is selected from the group consisting of

(1) -CO(R¹⁹)- or -(R¹⁹)CO-, wherein R¹⁹ is
a heterocycloalkyl, or a cycloalkyl
30 group;

-50-

- (2) -CONH- or -HNCO-; and
(3) -CO-;
(4) -SO₂-R¹⁹- or -R¹⁹-SO₂-;
(5) -SO₂-;
5 (6) -NH-SO₂- or -SO₂-NH-; or
(7) E is absent and R is bonded directly to Y; and

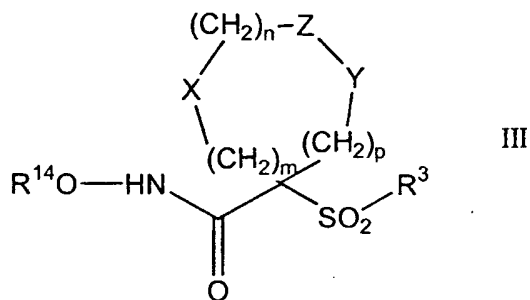
Y is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl,
10 aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a
15 aminoalkyl group, wherein the aryl or heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, and an amino
20 group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

The substituent -G-A-R-E-Y preferably contains
25 two to four carbocyclic or heterocyclic rings, including the aryl or heteroaryl group, G. More preferably, each of those rings is 6-membered. Additional separate preferences for a compound of formula II include: (a) that A is -O- or -S-, (b) R
30 is an aryl, heteroaryl, cycloalkyl or

-51-

heterocycloalkyl group, (c) E is absent, and (d) Y is selected from the group consisting of hydrido, an alkyl, alkoxy, perfluoroalkoxy and a perfluoroalkylthio group.

- 5 A more preferred compound for use in a contemplated process has a structure that corresponds to formula III, below:



10

- wherein R³ is a single-ringed aryl or heteroaryl group that is 5- or 6-membered, and is itself substituted at its own 4-position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring with a substituent selected from the group consisting of a thiophenoxy, 4-chloro-phenoxy, 3-chlorophenoxy, 4-methoxyphenoxy, 3-benzodioxol-5-yloxy, 3,4-dimethylphenoxy, 4-fluorophenoxy, 4-fluorothiophenoxy, phenoxy, 4-trifluoromethoxyphenoxy, 4-trifluoromethylphenoxy, 4-(trifluoromethylthio)phenoxy, 4-(trifluoromethylthio)thiophenoxy, 4-chloro-3-fluorophenoxy, 4-isopropoxyphenoxy, 4-isopropylphenoxy, (2-methyl-1,3-benzothiazol-5-yl)oxy, 4-(1H-imidazol-1-yl)phenoxy, 4-chloro-3-methylphenoxy, 3-methyl-phenoxy, 4-ethoxyphenoxy, 3,4-difluorophenoxy, 4-chloro-3-methylphenoxy, 4-fluoro-3-chlorophenoxy, 4-(1H-1,2,4-
- 15
- 20
- 25

triazol-1-yl)phenoxy, 3,5-difluorophenoxy, 3,4-dichlorophenoxy, 4-cyclopentylphenoxy, 4-bromo-3-methylphenoxy, 4-bromophenoxy, 4-methylthiophenoxy, 4-phenylphenoxy, 4-benzylphenoxy, 6-quinolinyl, 4-amino-3-methylphenoxy, 3-methoxyphenoxy, 5,6,7,8-tetrahydro-2-naphthalenyloxy, 3-hydroxymethylphenoxy, and a 4-benzyloxyphenoxy group;

R^{14} is hydrido, a pharmaceutically acceptable cation or $C(W)R^{15}$ where W is O or S and R^{15} is selected from the group consisting of an C_1 - C_6 -alkyl, aryl, C_1 - C_6 -alkoxy, heteroaryl- C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, aryloxy, ar- C_1 - C_6 -alkoxy, ar- C_1 - C_6 -alkyl, heteroaryl and amino C_1 - C_6 -alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group consisting of an C_1 - C_6 -alkyl, aryl, ar- C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, ar- C_1 - C_6 -alkoxycarbonyl, C_1 - C_6 -alkoxycarbonyl, and a C_1 - C_6 -alkanoyl radical, or (iii) wherein the amino C_1 - C_6 -alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocycle or heteroaryl ring;

m is zero, 1 or 2;

n is zero, 1 or 2;

p is zero, 1 or 2;

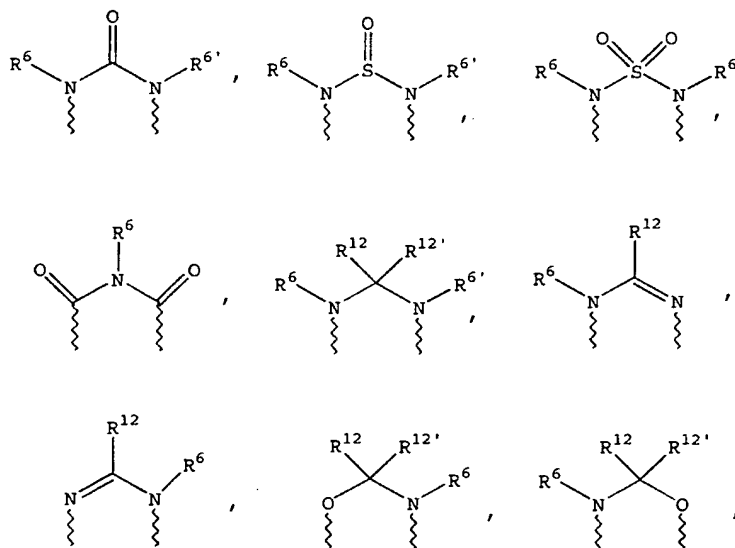
the sum of $m + n + p = 1, 2, 3$ or 4;

(a) one of X, Y and Z is selected from the group consisting of $C(O)$, NR^6 , O, S, $S(O)$, $S(O)_2$ and

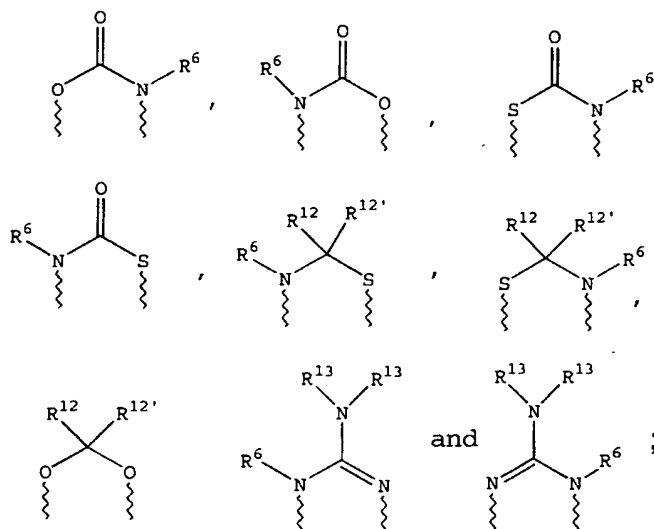
$\text{NS(O)}_2\text{R}^7$, and the remaining two of X, Y and Z are CR^8R^9 , and $\text{CR}^{10}\text{R}^{11}$, or

(b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting
 5 of $\text{NR}^6\text{C(O)}$, $\text{NR}^6\text{S(O)}$, $\text{NR}^6\text{S(O)}_2$, NR^6S , NR^6O , SS , NR^6NR^6 and OC(O) , with the remaining one of X, Y and Z being CR^8R^9 , or

(c) n is zero and X, Y and Z together constitute a moiety selected from the group
 10 consisting of



- 54 -



wherein wavy lines are bonds to the atoms of the depicted ring;

- 5 R^6 and $\text{R}^{6'}$ are independently selected from the group consisting of hydrido, C_1 - C_6 -alkanoyl, C_6 -aryl- C_1 - C_6 -alkyl, aroyl, bis(C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl)- C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -perfluoroalkyl, C_1 - C_6 -trifluoromethylalkyl, C_1 - C_6 -perfluoroalkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl, C_3 - C_8 -heterocycloalkyl, C_3 - C_8 -heterocycloalkylcarbonyl, C_6 -aryl, C_5 - C_6 -heterocyclo, C_5 - C_6 -heteroaryl, C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, C_6 -aryloxy- C_1 - C_6 -alkyl, heteroaryloxy- C_1 - C_6 -alkyl, heteroaryl- C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, heteroarylthio- C_1 - C_6 -alkyl, C_6 -arylsulfonyl, C_1 - C_6 -alkylsulfonyl, C_5 - C_6 -heteroarylsulfonyl, carboxy- C_1 - C_6 -alkyl, C_1 - C_4 -alkoxycarbonyl- C_1 - C_6 -alkyl, aminocarbonyl, C_1 - C_6 -alkyliminocarbonyl, C_6 -
- 10
- 15

aryliminocarbonyl, C₅-C₆-heterocycloiminocarbonyl, C₆-arylthio-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, C₆-arylthio-C₃-C₆-alkenyl, C₁-C₄-alkylthio-C₃-C₆-alkenyl, C₅-C₆-heteroaryl-C₁-C₆-alkyl, halo-C₁-C₆-alkanoyl, hydroxy-C₁-C₆-alkanoyl, thiol-C₁-C₆-alkanoyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₅-alkoxycarbonyl, aryloxycarbonyl, NR⁸R⁹-C₁-C₅-alkylcarbonyl, hydroxy-C₁-C₅-alkyl, an aminocarbonyl wherein the aminocarbonyl nitrogen is

10 (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group,

hydroxyaminocarbonyl, an aminosulfonyl group wherein

15 the aminosulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group, an amino-C₁-C₆-alkylsulfonyl

20 group wherein the amino-C₁-C₆-alkylsulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group and an amino-

25 C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group;

R^7 is selected from the group consisting of a benzyl, phenyl, C_1 - C_6 -alkyl, C_3 - C_6 -alkynyl, C_3 - C_6 -alkenyl and a C_1 - C_6 -hydroxyalkyl group;

R^8 and R^9 and R^{10} and R^{11} are independently
5 selected from the group consisting of a hydrido, hydroxy, C_1 - C_6 -alkyl, aryl, ar- C_1 - C_6 -alkyl, heteroaryl, heteroar- C_1 - C_6 -alkyl, C_2 - C_6 -alkynyl, C_2 - C_6 -alkenyl, thiol- C_1 - C_6 -alkyl, C_1 - C_6 -alkylthio- C_1 - C_6 -alkyl cycloalkyl, cycloalkyl- C_1 - C_6 -alkyl,
10 heterocycloalkyl- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, aralkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, hydroxy- C_1 - C_6 -alkyl, hydroxycarbonyl- C_1 - C_6 -alkyl, hydroxycarbonylar- C_1 - C_6 -alkyl, aminocarbonyl- C_1 - C_6 -alkyl, aryloxy- C_1 - C_6 -alkyl, heteroaryloxy- C_1 - C_6 -alkyl, arylthio- C_1 - C_6 -alkyl, heteroarylthio- C_1 - C_6 -alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro- C_1 - C_6 -alkyl, trifluoromethyl- C_1 - C_6 -alkyl, halo- C_1 - C_6 -alkyl, alkoxycarbonylamino- C_1 - C_6 -alkyl and an amino-
15 C_1 - C_6 -alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C_1 - C_6 -alkyl, ar- C_1 - C_6 -alkyl, cycloalkyl and C_1 - C_6 -alkanoyl, or wherein R^8 and R^9 or R^{10} and
20 R^{11} and the carbon to which they are bonded form a carbonyl group, or wherein R^8 and R^9 or R^{10} and R^{11} , or R^8 and R^{10} together with the atoms to which they are bonded form a 5- to 8-membered carbocyclic ring,

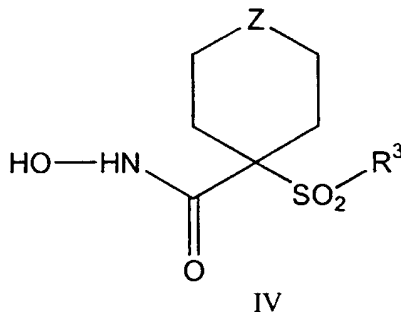
or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or sulfur, with the proviso that only one of R⁸ and R⁹ or R¹⁰ and R¹¹ is hydroxy;

- 5 R¹² and R^{12'} are independently selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroaralkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-
10 C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl,
15 heteroaryloxy-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-
20 C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl; and
25 R¹³ is selected from the group consisting of a hydrido, benzyl, phenyl, C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl and a C₁-C₆-hydroxyalkyl group. Again, the use of a compound of formula III as a

pharmaceutically acceptable salt is also contemplated.

Preferences related to a compound of formula III that also apply to a compound of formula II include the following, which are independently preferred: (a) the sum of $m + n + p = 1$ or 2 , and more preferably 2 ; (b) Z is O , S or NR^6 ; (c) R^6 is selected from the group consisting of C_3 - C_6 -cycloalkyl, C_1 - C_6 -alkyl, C_3 - C_6 -alkenyl, C_3 - C_6 -alkynyl, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, amino- C_1 - C_6 -alkyl, aminosulfonyl, heteroaryl- C_1 - C_6 -alkyl, aryloxycarbonyl, and C_1 - C_6 -alkoxycarbonyl; and (d) $m = n = \text{zero}$, $p = 1$, and Y is NR^6 . Another preference for a compound of both of formulas II and III is that R^{14} be hydrido, or that W of the $C(W)R^{15}$ pro-drug form be O and R^{15} be a C_1 - C_6 -alkyl, aryl, C_1 - C_6 -alkoxy, heteroaryl- C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl- C_1 - C_6 -alkyl, or aryloxy group.

A still more preferred compound for use in a contemplated process corresponds in structure to formula IV, below:



Here, R^3 is as defined above as to formulas I, III and more preferably as defined as to formula II

(wherein the R^3 radical is the substituent G-A-R-E-Y). Most preferably, R^3 is as defined in formula III.

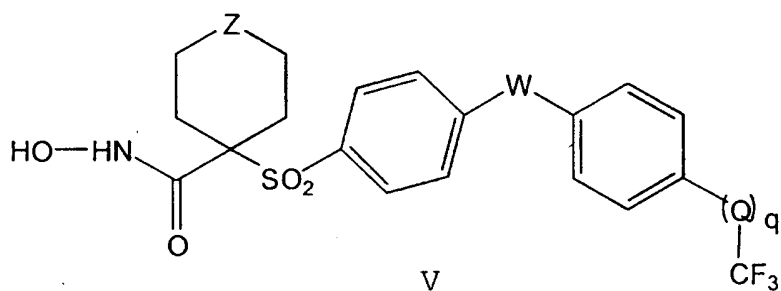
Z is selected group the group consisting of O,
5 S, NR^6 , SO, SO_2 , and NSO_2R^7 ,

wherein R^6 is selected from the group consisting of hydrido, C_1 - C_5 -alkyl, C_1 - C_5 -alkanoyl, benzyl, benzoyl, C_3 - C_5 -alkynyl, C_3 - C_5 -alkenyl, C_1 - C_3 -alkoxy- C_1 - C_4 -alkyl, C_3 - C_6 -cycloalkyl, heteroaryl- C_1 - C_6 -
10 alkyl, C_1 - C_5 -hydroxyalkyl, C_1 - C_5 -carboxyalkyl, C_1 - C_5 -alkoxy C_1 - C_5 -alkylcarbonyl, and NR^8R^9 - C_1 - C_5 -alkylcarbonyl or NR^8R^9 - C_1 - C_5 -alkyl wherein R^8 and R^9 are independently hydrido, C_1 - C_5 -alkyl, C_1 - C_5 -alkoxycarbonyl or aryl- C_1 - C_5 -alkoxycarbonyl, or NR^8R^9
15 together form a heterocyclic ring containing 5- to 8-atoms in the ring; and

R^7 is selected from the group consisting of an arylalkyl, aryl, heteroaryl, heterocyclo, C_1 - C_6 -alkyl, C_3 - C_6 -alkynyl, C_3 - C_6 -alkenyl, C_1 - C_6 -
20 carboxyalkyl and a C_1 - C_6 -hydroxyalkyl group. Most preferably, Z is O or NR^6 . Here too, the use of a compound of formula IV as a pharmaceutically acceptable salt is contemplated.

A still more preferred group of contemplated
25 compounds for use in a contemplated process correspond in structure to formula V, below;

-60-



wherein

Z is as previously defined for formula IV;

5 W and Q are independently oxygen (O), NR^6 or

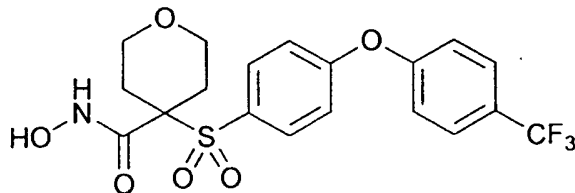
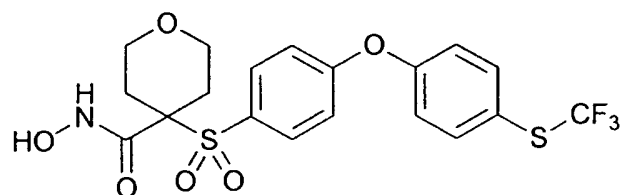
sulfur (S), and R^6 is as defined in formula IV; and

q is zero or one such that when q is zero, Q is absent and the trifluoromethyl group is bonded directly to the depicted phenyl ring. Here again, the

10 use of a compound of formula IV as a pharmaceutically acceptable salt is contemplated.

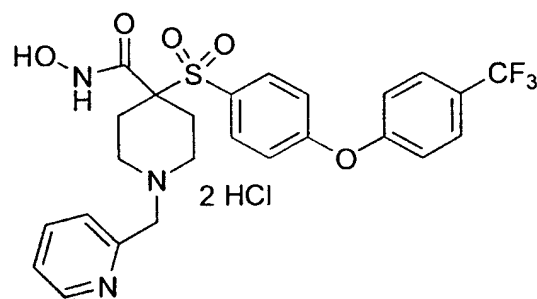
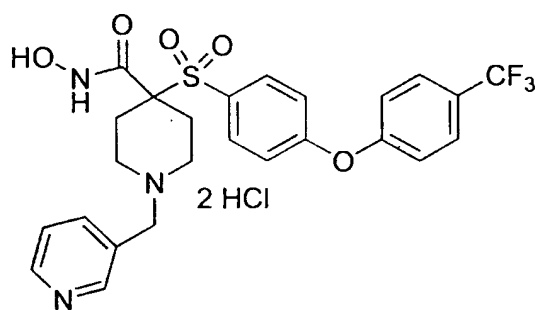
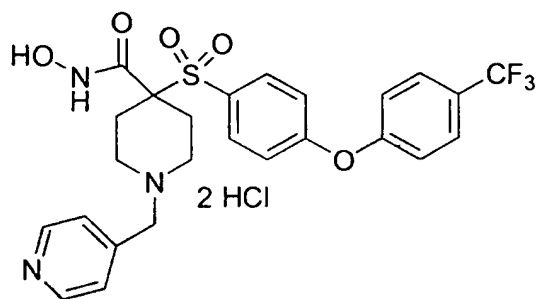
Particularly preferred compounds within the group defined by formula V have the structural formulas shown below:

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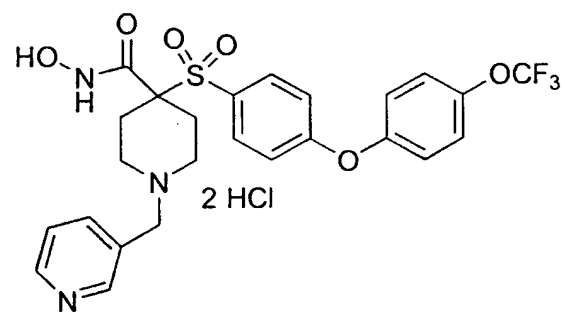


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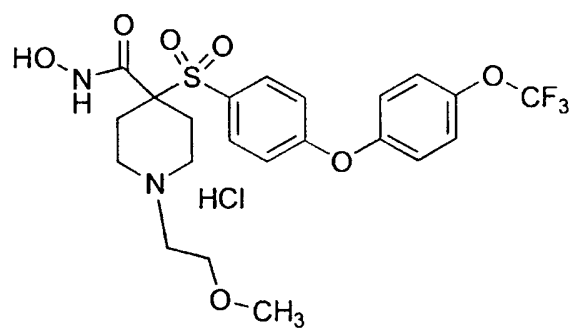
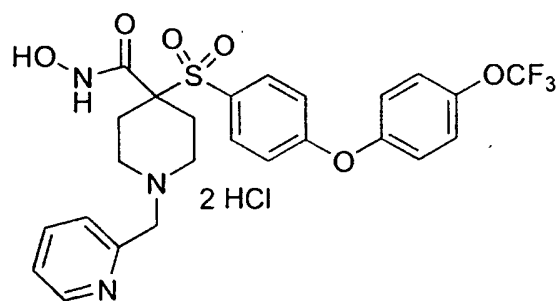
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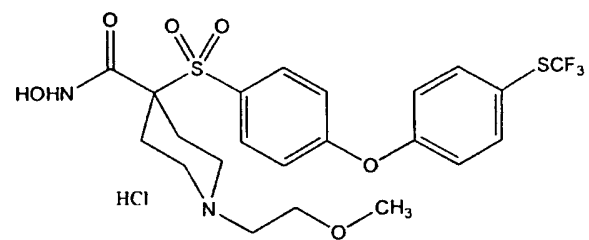
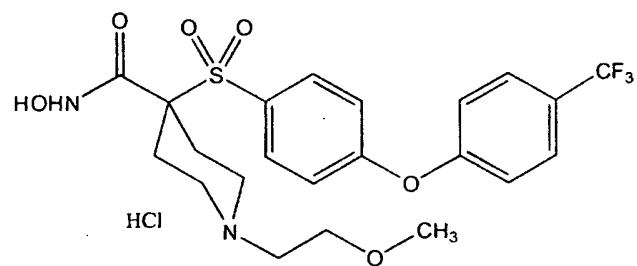
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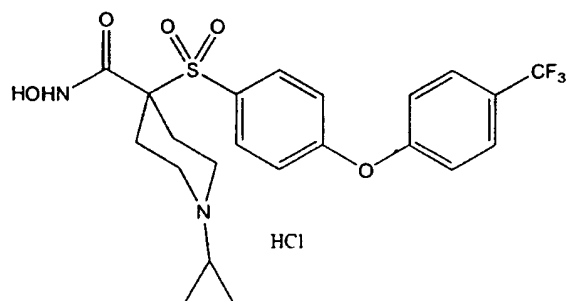
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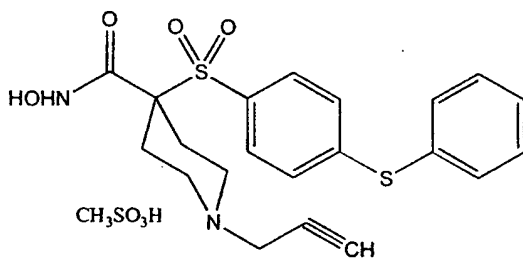
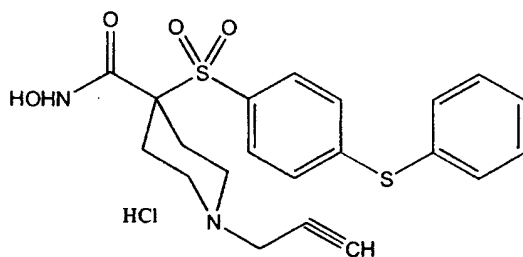
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Also particularly preferred are the following
5 compounds:



10

Several particularly preferred compounds whose structures correspond to formulas I through V are illustrated in the Tables and examples provided hereinafter.

15 As was noted before, the compounds of formulas II, III, IV and V, and their pharmaceutically acceptable salts are themselves contemplated compounds of the invention.

In preferred practice, an SO₂-linked R³ radical is an aryl or heteroaryl group that is a 5- or 6-membered single-ring that is itself substituted with one other single-ringed aryl or heteroaryl group or, with an alkyl or alkoxy group having a chain length of 3 to about 16 carbon atoms (and more preferably a length of up to about 14 carbon atoms), a phenoxy group, a thiophenoxy [C₆H₅-S-] group, a phenylazo [C₆H₅-N₂-] group, a N-piperidyl [C₅H₁₀N-] group, a N-piperazyl [NC₄H₉N-] group or a benzamido [-NHC(O)C₆H₅] group. The SO₂-linked single-ringed aryl or heteroaryl R³ group here is substituted at its own 4-position when a 6-membered ring and at its own 3- or 4-position when a 5-membered ring.

The SO₂-linked aryl or heteroaryl group of a R³ radical is preferably itself substituted at the 4-position when a 6-membered ring or the 3- or 4-position when a 5-membered ring. A particularly preferred substituent is a single-ringed aryl or heteroaryl, phenoxy, thiophenoxy, phenylazo, N-piperidyl, N-piperazyl or benzamido group that is unsubstituted or can itself be substituted.

The 4- and 3-positions of rings discussed here are numbered from the sites of substituent bonding as compared to formalized ring numbering positions used in heteroaryl nomenclature, as is discussed further hereinbelow. Here, single atoms such as halogen moieties (fluoro, chloro, bromo, or iodo) or substituents that contain one to a chain length of about five atoms other than hydrogen such as phenyl, C₁-C₄ alkyl, trifluoromethyl,

trifluoromethoxy, trifluorothiomethyl or carboxyethyl groups are preferred, although longer substituents can be accommodated up to a total length of an icosyl group.

5 Exemplary particularly preferred substituted SO₂-linked R³ radicals include 4-(phenyl)phenyl [biphenyl], 4-(4'-methoxyphenyl)-phenyl, 4-(phenoxy)phenyl, 4-(thiophenyl)phenyl [4-(phenylthio)phenyl], 4-(azophenyl)phenyl, 4-[(4'-
10 trifluoromethylthio)phenoxy]phenyl, 4-[(4'-trifluoromethylthio)thiophenyl]phenyl, 4-[(4'-trifluoromethyl)phenoxy]phenyl, 4-[(4'-trifluoromethyl)thiophenyl]phenyl, 4-[(4'-trifluoromethoxy)phenoxy]phenyl, 4-[(4'-
15 trifluoromethoxy)thiophenyl]phenyl, 4-[(4'-phenyl)N-piperidyl]phenyl, 4-[(4'-acetyl)N-piperazyl]phenyl and 4-(benzamido)phenyl.

Inasmuch as a contemplated SO₂-linked aryl or heteroaryl radical of an R³ group is itself
20 preferably substituted with a 6-membered ring, two nomenclature systems are used together herein for ease in understanding substituent positions. The first system uses position numbers for the ring directly bonded to the SO₂-group, whereas the second
25 system uses ortho, meta or para for the position of one or more substituents of a 6-membered ring bonded to a SO₂-linked aryl or heteroaryl radical. Although ortho, meta and para positional nomenclature is normally not used with aliphatic ring systems, it is
30 believed more readily understood for describing the present compounds when used in conjunction with the numerical system for the first ring bonded to the

SO₂-group. When a R³ radical is other than a 6-membered ring, substituent positions are numbered from the position of linkage to the aromatic or heteroaromatic ring. Formal chemical nomenclature is
5 used in naming particular compounds.

Thus, the 1-position of an above-discussed SO₂-linked aryl or heteroaryl group is the position at which the SO₂-group is bonded to the ring. The 4- and 3-positions of rings discussed here are numbered
10 from the sites of substituent bonding from the SO₂-linkage as compared to formalized ring numbering positions used in heteroaryl nomenclature.

When examined along its longest chain of atoms, an R³ radical including its own substituent
15 has a total length that is greater than a saturated chain of five carbon atoms (a pentyl group), and preferably has a length greater than that of a saturated chain of six carbon atoms (a hexyl group); i.e., a length of about a heptyl chain or longer. An
20 R³ radical also has a length that is less than that of a saturated chain of about 20 carbon atoms [an icosyl group (icosyl was formerly spelled eicosyl)] and more preferably about 18 carbon atoms (a stearyl group). Most preferably, the length of R³ is about
25 that of an 8 to about 12 carbon atom chain, even though many more atoms may be present in ring structures or substituents. This length requirement is discussed further below.

Looked at more generally, and aside from
30 specific moieties from which it is constructed, an R³ radical (group or moiety) has a length that is

greater than that of a pentyl group. Such an R^3 radical also has a length that is less than that of an icosyl (didecyl) group. That is to say that R^3 is a radical having a minimal length longer than a saturated five carbon chain, and preferably greater than a hexyl group, but is shorter than the length of a saturated twenty carbon atom chain, and preferably shorter than an eighteen carbon chain. Most preferably, R^3 has a length greater than that of an octyl group and less than that of a lauryl group.

More specifically, an R^3 group has a minimal length of a hexyl group only when that substituent is comprised of two rings that can be fused or simply covalently linked together by exocyclic bonding. When R^3 does not contain two linked or fused rings, e.g., where a R^3 radical includes an alkyl or second, third or fourth ring substituent, R^3 has a length that is greater than that of a hexyl group. Exemplary of such two ring groups are a 2-naphthyl group or a 2-quinolinyl group (each with a six carbon chain length) and 8-purinyl (with a five carbon atom chain length). Without wishing to be bound by theory, it is believed that the presence of multiple rings in R^3 enhances selectivity of the enzyme activity inhibitor profile.

The radical chain lengths are measured along the longest linear atom chain in the radical, following the skeletal atoms around a ring where necessary. Each atom in the chain, e.g. carbon, oxygen, sulfur or nitrogen, is presumed to be carbon for ease in calculation.

Such lengths can be readily determined by using published bond angles, bond lengths and atomic radii, as needed, to draw and measure a desired, usually staggered, chain, or by building models using
5 commercially available kits whose bond angles, lengths and atomic radii are in accord with accepted, published values. Radical (substituent) lengths can also be determined somewhat less exactly by assuming that all atoms have bond lengths saturated carbon,
10 that unsaturated bonds have the same lengths as saturated bonds and that bond angles for unsaturated bonds are the same as those for saturated bonds, although the above-mentioned modes of measurement are preferred. For example, a phenyl or pyridyl group
15 has a length of a four carbon chain, as does a propoxy group, whereas a biphenyl group has a length of about an eight carbon chain using such a measurement mode.

In addition, a R^3 group when rotated about
20 an axis drawn through the SO_2 -bonded 1-position and the 4-position of a 6-membered ring or the SO_2 -bonded position and substituent-bonded 3- or 4-position of a 5-membered ring defines a three-dimensional volume whose widest dimension has the width of about one
25 furanyl ring to about two phenyl rings in a direction transverse to that axis to rotation.

Thus, a 2-naphthyl substituent or an 8-purinyll substituent is an appropriately sized R^3 group when examined using the above rotational width
30 criterion as well as the before-discussed criterion. On the other hand, a 1-naphthyl group or a 7- or 9-

purinyl group is too wide upon rotation and is excluded from being an R^3 group.

As a consequence of these length and width requirements, R^3 radicals such as 4-(phenyl)phenyl
5 [biphenyl], 4-(4'-methoxyphenyl)-phenyl, 4-(phenoxy)phenyl, 4-(thiophenyl)phenyl [4-(phenylthio)phenyl], 4-(azophenyl)phenyl, 4-[(4'-trifluoromethylthio)phenoxy]phenyl, 4-[(4'-trifluoromethylthio)thiophenyl]phenyl, 4-[(4'-trifluoromethyl)phenoxy]phenyl, 4-[(4'-trifluoromethyl)thiophenyl]phenyl, 4-[(4'-trifluoromethoxy)phenoxy]phenyl, 4-[(4'-trifluoromethoxy)thiophenyl]phenyl, 4-[(4'-phenyl)N-piperidyl]phenyl, 4-[(4'-acetyl)N-piperazyl]phenyl
10 and 4-(benzamido)phenyl are particularly preferred R^3 radicals. Those substituents can themselves also be substituted in the second ring from the SO_2 group at the meta- or para-position or both with a single atom or a substituent containing a longest chain length
15 that is preferably of up to five atoms, excluding hydrogen.

Without wishing to be bound by theory, the length of a R^3 radical substituent bonded to the SO_2 group is believed to play a role in the overall
25 activity of a contemplated inhibitor compound against MMP enzymes generally. The length of the R^3 radical group also appears to play a role in the selective activity of an inhibitor compound against particular MMP enzymes.

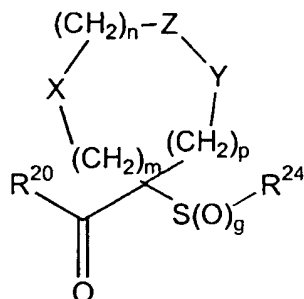
30 In particularly preferred practice, R^3 is a PhR^{23} group, wherein Ph is phenyl. The phenyl ring

(Ph) of a PhR^{23} group is substituted at its para-position (4-position) by an R^{23} group that can be another single-ringed aryl or heteroaryl group, a piperidyl group, a piperazinyl group, a phenoxy group, a thiophenoxy [$\text{C}_6\text{H}_5\text{-S-}$] group, a phenylazo [$\text{C}_6\text{H}_5\text{-N}_2\text{-}$] group or a benzamido [$\text{-NHC(O)C}_6\text{H}_5$] group.

In one embodiment of a particularly preferred aromatic sulfone hydroxamate inhibitor compound, an R^{23} substituent is phenoxy and is itself substituted at its own para-position with a moiety that is selected from the group consisting of a halogen, a $\text{C}_1\text{-C}_4$ alkoxy group, a $\text{C}_1\text{-C}_4$ alkyl group, a dimethylamino group, a carboxyl $\text{C}_1\text{-C}_3$ alkylene group, a $\text{C}_1\text{-C}_4$ alkoxy carbonyl $\text{C}_1\text{-C}_3$ alkylene group, a trifluoromethylthio group, a trifluoromethoxy group, a trifluoromethyl group and a carboxamido $\text{C}_1\text{-C}_3$ alkylene group, or is substituted at the meta- and para-positions by a methylenedioxy group. It is to be understood that any R^{23} substituent can be substituted with a moiety from the above list. Such substitution at the para-position is preferred.

The present invention also contemplates a compound that corresponds in structure to formula VI, below, that is useful in preparing a compound of formulas I-V, as well as as an active MMP-inhibiting compound and as a pro-drug form of an inhibitor.

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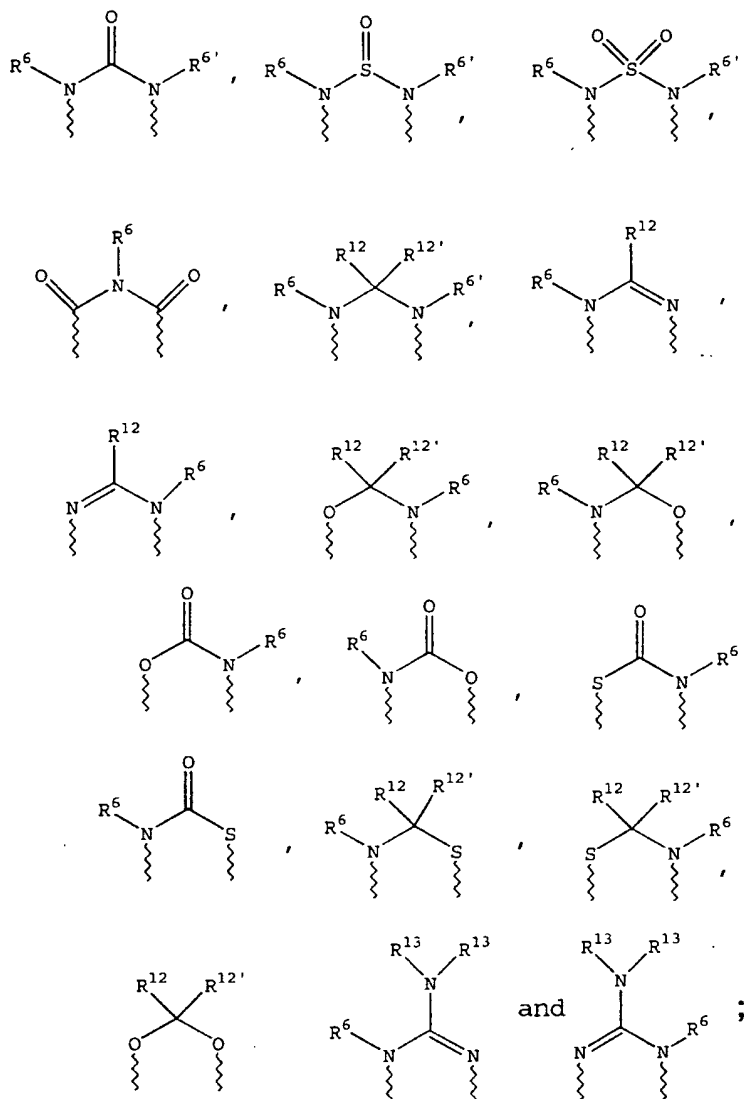
VI

wherein g is zero, 1 or 2;

- 5 R^{20} is (a) $-O-R^{21}$, where R^{21} is selected from the group consisting of a hydrido, C_1-C_6 -alkyl, aryl, ar- C_1-C_6 -alkyl group and a pharmaceutically acceptable cation, (b) $-NH-O-R^{22}$ wherein R^{22} is a selectively removable protecting group such as a 2-
- 10 tetrahydropyranyl, benzyl, p-methoxybenzyl (MOZ), carbonyl- C_1-C_6 -alkoxy, trisubstituted silyl group or o-nitrophenyl group, peptide synthesis resin and the like, wherein the trisubstituted silyl group is substituted with C_1-C_6 -alkyl, aryl, or ar- C_1-C_6 -alkyl
- 15 or a mixture thereof, (c) $-NH-O-R^{14}$, where R^{14} is hydrido, a pharmaceutically acceptable cation or $C(W)R^{25}$ where W is O (oxo) or S (thioxo) and R^{25} is selected from the group consisting of an C_1-C_6 -alkyl, aryl, C_1-C_6 -alkoxy, heteroaryl- C_1-C_6 -alkyl, C_3-C_8 -
- 20 cycloalkyl- C_1-C_6 -alkyl, aryloxy, ar- C_1-C_6 -alkoxy, ar- C_1-C_6 -alkyl, heteroaryl and amino C_1-C_6 -alkyl group wherein the amino C_1-C_6 -alkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two substituents independently selected from the group

- consisting of an C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl-C₁-C₆-alkyl, ar-C₁-C₆-alkoxycarbonyl, C₁-C₆-alkoxycarbonyl, and C₁-C₆-alkanoyl radical, or (iii) wherein the amino C₁-C₆-
- 5 alkyl nitrogen and two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring, or (d) -NR²⁶R²⁷, where R²⁶ and R²⁷ are independently selected from the group consisting of a hydrido, C₁-C₆-alkyl, amino C₁-C₆-alkyl, hydroxy C₁-
- 10 C₆-alkyl, aryl, ar-C₁-C₆-alkyl group, or R²⁶ and R²⁷ together with the depicted nitrogen atom form a 5- to 7-membered ring containing zero or one additional heteroatom that is oxygen, nitrogen or sulfur;
- m is zero, 1 or 2;
- 15 n is zero, 1 or 2;
- p is zero, 1 or 2;
- the sum of m + n + p = 1, 2, 3 or 4;
- (a) one of X, Y and Z is selected from the group consisting of C(O), NR⁶, O, S, S(O), S(O)₂ and
- 20 NS(O)₂R⁷, and the remaining two of X, Y and Z are CR⁸R⁹, and CR¹⁰R¹¹, or
- (b) X and Z or Z and Y together constitute a moiety that is selected from the group consisting of NR⁶C(O), NR⁶S(O), NR⁶S(O)₂, NR⁶S, NR⁶O, SS, NR⁶NR⁶
- 25 and OC(O), with the remaining one of X, Y and Z being CR⁸R⁹, or
- (c) n is zero and X, Y and Z together constitute a moiety selected from the group consisting of

- 73 -



wherein wavy lines are bonds to the atoms of the
 5 depicted ring;

R^6 and $R^{6'}$ are independently selected from the
 group consisting of hydrido, C_1 - C_6 -alkanoyl, C_6 -aryl-
 C_1 - C_6 -alkyl, aroyl, bis(C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl)- C_1 -
 C_6 -alkyl, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -
 10 perfluoroalkyl, C_1 - C_6 -trifluoromethylalkyl, C_1 - C_6 -
 perfluoroalkoxy- C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_6 -

- alkyl, C₃-C₆-cycloalkyl, C₃-C₈-heterocycloalkyl, C₃-C₈-heterocycloalkylcarbonyl, C₆-aryl, C₅-C₆-heterocyclo, C₅-C₆-heteroaryl, C₃-C₈-cycloalkyl-C₁-C₆-alkyl, C₆-aryloxy-C₁-C₆-alkyl, heteroaryloxy-C₁-C₆-alkyl, heteroaryl-C₁-C₆-alkoxy-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, C₆-arylsulfonyl, C₁-C₆-alkylsulfonyl, C₅-C₆-heteroarylsulfonyl, carboxy-C₁-C₆-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₆-alkyl, aminocarbonyl, C₁-C₆-alkyliminocarbonyl, C₆-aryliminocarbonyl, C₅-C₆-heterocycloiminocarbonyl, C₆-arylthio-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, C₆-arylthio-C₃-C₆-alkenyl, C₁-C₄-alkylthio-C₃-C₆-alkenyl, C₅-C₆-heteroaryl-C₁-C₆-alkyl, halo-C₁-C₆-alkanoyl, hydroxy-C₁-C₆-alkanoyl, thiol-C₁-C₆-alkanoyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₅-alkoxycarbonyl, aryloxycarbonyl, NR⁸R⁹-C₁-C₅-alkylcarbonyl, hydroxy-C₁-C₅-alkyl, an aminocarbonyl wherein the aminocarbonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group, hydroxyaminocarbonyl, an aminosulfonyl group wherein the aminosulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-cycloalkyl and a C₁-C₆-alkanoyl group, an amino-C₁-C₆-alkylsulfonyl

group wherein the amino-C₁-C₆-alkylsulfonyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-
5 cycloalkyl and a C₁-C₆-alkanoyl group and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, C₃-C₈-
10 cycloalkyl and a C₁-C₆-alkanoyl group;

R⁷ is selected from the group consisting of a benzyl, phenyl, C₁-C₆-alkyl, C₃-C₆-alkynyl, C₃-C₆-alkenyl and a C₁-C₆-hydroxyalkyl group;

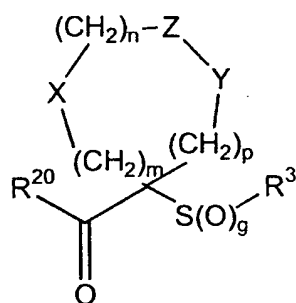
R⁸ and R⁹ and R¹⁰ and R¹¹ are independently
15 selected from the group consisting of a hydrido, hydroxy, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroar-C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl cycloalkyl, cycloalkyl-C₁-C₆-alkyl,
20 heterocycloalkyl-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aralkoxy-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-
25 alkyl, heteroaryloxy-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-C₁-C₆-alkyl, halo-C₁-C₆-

- alkyl, alkoxy-carbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group
- 5 consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹ and the carbon to which they are bonded form a carbonyl group, or wherein R⁸ and R⁹ or R¹⁰ and R¹¹, or R⁸ and R¹⁰ together with the atoms to which they
- 10 are bonded form a 5- to 8-membered carbocyclic ring, or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are nitrogen, oxygen, or sulfur, with the proviso that only one of R⁸ and R⁹ or R¹⁰ and R¹¹ is hydroxy;
- 15 R¹² and R^{12'} are independently selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl, heteroaryl, heteroaralkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl, thiol-C₁-C₆-alkyl, cycloalkyl, cycloalkyl-C₁-C₆-alkyl, heterocycloalkyl-
- 20 C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl, amino-C₁-C₆-alkyl, C₁-C₆-alkoxy-C₁-C₆-alkoxy-C₁-C₆-alkyl, hydroxy-C₁-C₆-alkyl, hydroxycarbonyl-C₁-C₆-alkyl, hydroxycarbonylar-C₁-C₆-alkyl, aminocarbonyl-C₁-C₆-alkyl, aryloxy-C₁-C₆-alkyl,
- 25 heteroaryloxy-C₁-C₆-alkyl, C₁-C₆-alkylthio-C₁-C₆-alkyl, arylthio-C₁-C₆-alkyl, heteroarylthio-C₁-C₆-alkyl, the sulfoxide or sulfone of any said thio substituents, perfluoro-C₁-C₆-alkyl, trifluoromethyl-

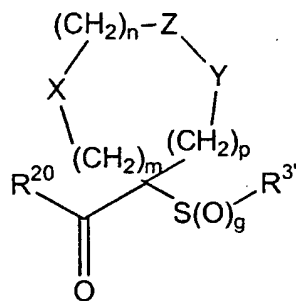
C₁-C₆-alkyl, halo-C₁-C₆-alkyl, alkoxycarbonylamino-C₁-C₆-alkyl and an amino-C₁-C₆-alkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted or (ii) substituted with one or two radicals independently
 5 selected from the group consisting of C₁-C₆-alkyl, ar-C₁-C₆-alkyl, cycloalkyl and C₁-C₆-alkanoyl;

R¹³ is selected from the group consisting of a hydrido, benzyl, phenyl, C₁-C₆-alkyl, C₂-C₆-alkynyl, C₂-C₆-alkenyl and a C₁-C₆-hydroxyalkyl group; and

10 R²⁴ is R³ as defined in formulas I, III, IV or is the substituent G-A-R-E-Y of formula II (formula VIA). Alternatively, R²⁴ is R^{3'}, an aryl or heteroaryl group that is substituted with a coupling substituent reactive for coupling with another moiety
 15 (formula VIB), such as a nucleophilically displaceable leaving group, D.



VIA



VIB

Exemplary nucleophilically displaceable leaving
 20 groups, D, include a halo (fluoro, chloro, bromo, or iodo) nitro, azido, phenylsulfoxido, aryloxy, C₁-C₆-alkoxy, a C₁-C₆-alkylsulfonate or arylsulfonate group and a trisubstituted ammonium group in which the

three substituents are independently aryl, ar- C₁-C₆-alkyl or C₁-C₆-alkyl. Additional coupling substituents include, without limitation, a hydroxyl group and an amino group that can be coupled with
5 carbonyl-containing moieties to form esters, urethanes, carbonates, amides and ureas. Similarly, a carboxyl coupling substituent can be used to form an ester, thioester or amide. Thus, a coupling substituent is useful in converting a coupling
10 substituent-containing aryl or heteroaryl group into a substituent such as a G-A-R-E-Y substituent discussed hereinabove by the formation of a covalent bond.

A compound of formula VI can be coupled with
15 another moiety at the R^{3'} coupling substituent to form a compound whose newly formed R³ group is that of formulas I, III, IV or -G-A-R-E-Y. Exemplary of such couplings are the nucleophilic displacement to form ethers and thioethers, as well as the formation
20 of ester, amide, urea, carbonate, urethane and the like linkages.

More particularly, where a R²⁰ group is -O-R²¹, with R²¹ being selected from the group consisting of a hydrido, C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl group and a pharmaceutically acceptable cation,
25 a precursor carboxylic acid or ester compound is defined that can be readily transformed into a hydroxamic acid, as is illustrated in several examples hereinafter.

30 Where a R²⁰ group is -NH-O-R²², wherein R²² is a selectively removable protecting group such as a

2-tetrahydropyranyl, benzyl, p-methoxybenzyl (MOZ), carbonyl-C₁-C₆-alkoxy, trisubstituted silyl group, an o-nitrophenyl group, or a peptide synthesis resin and the like, a synthetic intermediate is typically defined. In these compounds, a trisubstituted silyl group is substituted with C₁-C₆-alkyl, aryl, ar-C₁-C₆-alkyl or a mixture thereof, such as a trimethylsilyl, dimethylisopropylsilyl, triethylsilyl, triphenylsilyl, t-butyldiphenylsilyl, diphenylmethylsilyl, a tribenzylsilyl group, and the like. Exemplary trisubstituted silyl protecting groups and their uses are discussed at several places in Greene et al., Protective Groups In Organic Synthesis, 2nd ed., John Wiley & Sons, Inc., New York (1991).

A contemplated peptide synthesis resin is solid phase support also known as a so-called Merrifield's Peptide Resin that is adapted for synthesis and selective release of hydroxamic acid derivatives as is commercially available from Sigma Chemical Co., St. Louis, MO. An exemplary peptide synthesis resin so adapted and its use in the synthesis of hydroxamic acid derivatives is discussed in Floyd et al., *Tetrahedron Let.*, 37(44):8048-8048 (1996).

A 2-tetrahydropyranyl (THP) protecting group is a particularly preferred selectively removable protecting group. A contemplated THP-protected hydroxamate compound of formula VII can be prepared by reacting the carboxylic acid precursor compound of formula VII [where R²⁰ is -O-R²¹ and R²¹ is a hydrido group] in water with O-(tetrahydro-2H-

pyran-2-yl)hydroxylamine in the presence of N-methylmorpholine, N-hydroxybenzotriazole hydrate and a water-soluble carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The THP protecting group is readily removable in an aqueous acid solution such as an aqueous mixture of p-toluenesulfonic acid or HCl and acetonitrile or methanol. An illustrative THP-protected compound corresponds in structure to formula VIIB, below, wherein m, n, p, g, X, Z, Y, and D are as defined previously.

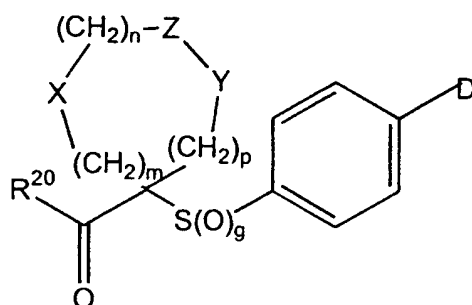
Where R^{20} is $-NR^{26}R^{27}$, and R^{26} and R^{27} are as defined before, an amide compound is defined that can be used as a precursor intermediate and surprisingly as a MMP inhibitor compound. R^{26} and R^{27} are both preferably hydrido.

Where a R^{20} group is $-NH-O-R^{14}$, and R^{14} is hydrido, or a pharmaceutically acceptable cation, an active hydroxamic acid or hydroxamate is defined.

Where a R^{20} group is $-NH-O-R^{14}$, and R^{14} is a $C(W)R^{25}$ group as defined before, a pro-drug form of the hydroxamic acid is defined that can form a hydroxamic acid or hydroxamate form of the inhibitor in situ.

A particularly preferred precursor intermediate to an intermediate compound of formula VI is an intermediate compound of formula VII, below

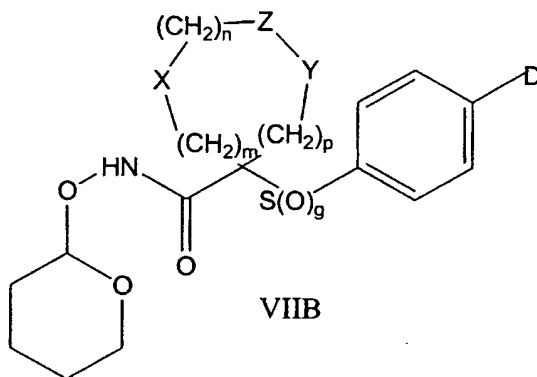
-81-



VII

wherein m , n , p , g , X , Z , Y , D and R^{20} are as defined above for formula VI.

5

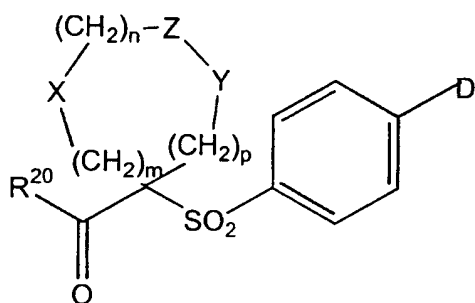


VIIB

In regard to a compound of each of formulas VI and VII, the subscript letter "g" is used to show the oxidation state of the sulfur atom. Where g is zero, the sulfur is unoxidized, and the compound depicted is typically the sulfide reaction product of a sulfur-containing synthon as is illustrated in the examples hereinafter. Where g is 1, the sulfur is oxidized to a sulfoxide, whereas when g is 2, the sulfur is oxidized to a sulfone as is also illustrated hereinafter. A compound of formulas VI or VII wherein g is zero or 1 as itself typically an intermediate in the formation of a similar compound

wherein g is 2 and the intermediate is a preferred sulfone.

A preferred intermediate corresponds in structure to formula VIIA, below, wherein R²⁰, X, Y, Z, m, n, p and D are as defined previously.



VIIA

In the written descriptions of molecules and groups, molecular descriptors can be combined to produce words or phrases that describe structural groups or are combined to describe structural groups. Such descriptors are used in this document. Common illustrative examples include such terms as aralkyl (or arylalkyl), heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, aralkoxyalkoxycarbonyl and the like. A specific example of a compound encompassed with the latter descriptor aralkoxyalkoxycarbonyl is C₆H₅-CH₂-CH₂-O-CH₂-O-(C=O)- wherein C₆H₅- is phenyl. It is also to be noted that a structural group can have more than one descriptive word or phrase in the art, for example, heteroaryloxyalkylcarbonyl can also be termed heteroaryloxyalkanoyl. Such combinations are used herein in the description of the processes, compounds and compositions of this invention and further examples are described below. The following

list is not intended to be exhaustive or drawn out but provide illustrative examples of words or phrases (terms) that are used herein.

As utilized herein, the term "alkyl", alone
5 or in combination, means a straight-chain or branched-chain alkyl radical containing 1 to about 12 carbon atoms, preferably 1 to about 10 carbon atoms, and more preferably 1 to about 6 carbon atoms. Examples of such radicals include methyl, ethyl, n-
10 propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like.

The term "alkenyl", alone or in combination, means a straight-chain or branched-chain
15 hydrocarbon radical having one or more double bonds and containing 2 to about 12 carbon atoms preferably 2 to about 10 carbon atoms, and more preferably, 2 to about 6 carbon atoms. Examples of suitable alkenyl radicals include ethenyl (vinyl), 2-propenyl, 3-
20 propenyl, 1,4-pentadienyl, 1,4-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, decenyl and the like.

The term "alkynyl", alone or in combination, means a straight-chain hydrocarbon radical having one or more triple bonds and
25 containing 2 to about 12 carbon atoms, preferably 2 to about 10 carbon atoms, and more preferably, 2 to about 6 carbon atoms. Examples of alkynyl radicals include ethynyl, 2-propynyl, 3-propynyl, decynyl, 1-butynyl, 2-butynyl, 3-butynyl, and the like.

30 The term "carbonyl" or "oxo", alone or in combination, means a -C(=O)- group wherein the remaining two bonds (valences) can be independently

substituted. The term carbonyl is also intended to encompass a hydrated carbonyl group $-C(OH)_2-$.

The term "thiol" or "sulfhydryl", alone or in combination, means a $-SH$ group. The term "thio" or "thia", alone or in combination, means a thiaether group; i.e., an ether group wherein the ether oxygen is replaced by a sulfur atom.

The term "amino", alone or in combination, means an amine or $-NH_2$ group whereas the term mono-substituted amino, alone or in combination, means a substituted amine $-N(H)(\text{substituent})$ group wherein one hydrogen atom is replaced with a substituent, and disubstituted amine means a $-N(\text{substituent})_2$ wherein two hydrogen atoms of the amino group are replaced with independently selected substituent groups.

Amines, amino groups and amides are compounds that can be designated as primary (I°), secondary (II°) or tertiary (III°) or unsubstituted, mono-substituted or N,N -disubstituted depending on the degree of substitution of the amino nitrogen. Quaternary amine (ammonium) (IV°) means a nitrogen with four substituents $[-N^+(\text{substituent})_4]$ that is positively charged and accompanied by a counter ion, whereas N -oxide means one substituent is oxygen and the group is represented as $[-N^+(\text{substituent})_3-O^-]$; i.e., the charges are internally compensated.

The term "cyano", alone or in combination, means a $-C$ -triple bond- N ($-C\equiv N$) group. The term "azido", alone or in combination, means a $-N$ -triple bond- N ($-N\equiv N$) group. The term "hydroxyl", alone or in combination, means a $-OH$ group. The term "nitro",

alone or in combination, means a -NO₂ group. The term "azo", alone or in combination, means a -N=N- group wherein the bonds at the terminal positions can be independently substituted.

5 The term "hydrazino", alone or in combination, means a -NH-NH- group wherein the depicted remaining two bonds (valences) can be independently substituted. The hydrogen atoms of the hydrazino group can be replaced, independently, with
10 substituents and the nitrogen atoms can form acid addition salts or be quaternized.

 The term "sulfonyl", alone or in combination, means a -SO₂- group wherein the depicted remaining two bonds (valences) can be independently
15 substituted. The term "sulfoxido", alone or in combination, means a -SO- group wherein the remaining two bonds (valences) can be independently substituted.

 The term "sulfone", alone or in
20 combination, means a -SO₂- group wherein the depicted remaining two bonds (valences) can be independently substituted. The term "sulfenamide", alone or in combination, means a -SON= group wherein the remaining three depicted bonds (valences) can be
25 independently substituted. The term "sulfide", alone or in combination, means a -S- group wherein the remaining two bonds (valences) can be independently substituted.

 The term "alkoxy", alone or in combination,
30 means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy,

isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

The term "cycloalkyl", alone or in combination, means a cyclic alkyl radical that
5 contains 3 to about 8 carbon atoms. The term "cycloalkylalkyl" means an alkyl radical as defined above that is substituted by a cycloalkyl radical containing 3 to about 8, preferably 3 to about 6, carbon atoms. Examples of such cycloalkyl radicals
10 include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

A heterocyclic (heterocyclo) or heterocycloportion of a heterocyclocarbonyl, heterocyclooxycarbonyl, heterocycloalkoxycarbonyl, or
15 heterocycloalkyl group or the like is a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle that contains one or more hetero atoms selected from nitrogen, oxygen and sulphur. Such a moiety can be optionally substituted
20 on one or more ring carbon atoms by halogen, alkyl, alkoxy, oxo, and the like, and/or on a secondary nitrogen atom (i.e., -NH-) of the ring by alkyl, aralkoxycarbonyl, alkanoyl, aryl or arylalkyl or on a tertiary nitrogen atom (i.e., =N-) by oxido and that
25 is attached via a carbon atom. The tertiary nitrogen atom with three substituents can also be attached to form a N-oxide [=N(O)-] group.

The term "aryl", alone or in combination, means a 5- or 6-membered carbocyclic aromatic ring-
30 containing moiety or a fused ring system containing two or three rings that have all carbon atoms in the ring; i.e., a carbocyclic aryl radical. Exemplary

carbocyclic aryl radicals include phenyl, indenyl and naphthyl radicals.

The term "heteroaryl", alone or in combination means a 5- or 6-membered aromatic ring-
5 containing moiety or a fused ring system (radical) containing two or three rings that have carbon atoms and also one or more heteroatoms in the ring(s) such as sulfur, oxygen and nitrogen. Examples of such heterocyclic or heteroaryl groups are pyrrolidinyl,
10 piperidyl, piperazinyl, morpholinyl, thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol-4-yl, 1-benzylloxycarbonylimidazol-4-yl, and the like), pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, furyl, tetrahydrofuryl, thienyl, triazolyl, oxazolyl,
15 oxadiazoyl, thiazolyl, thiadiazoyl, indolyl (e.g., 2-indolyl, and the like), quinolinyl, (e.g., 2-quinolinyl, 3-quinolinyl, 1-oxido-2-quinolinyl, and the like), isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, and the like), tetrahydroquinolinyl
20 (e.g., 1,2,3,4-tetrahydro-2-quinolyl, and the like), 1,2,3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, and the like), quinoxalinyl, β -carbolinyl, 2-benzofurancarbonyl, benzothiophenyl, 1-, 2-, 4- or 5-benzimidazolyl, and
25 the like radicals.

When an aryl or heteroaryl radical is a substituting moiety (group, substituent, or radical), it can itself substituted, the last-named substituent is independently selected from the group consisting
30 of a cyano, perfluoroalkyl, trifluoromethoxy, trifluoromethylthio, haloalkyl, trifluoromethylalkyl, aralkoxycarbonyl, aryloxycarbonyl, hydroxy, halo, alkyl, alkoxy, nitro,

thiol, hydroxycarbonyl, aryloxy, arylthio, aralkyl,
aryl, arylcarbonylamino, heteroaryloxy,
heteroarylthio, heteroaralkyl, cycloalkyl,
heterocyclooxy, heterocyclothio, heterocycloamino,
5 cycloalkyloxy, cycloalkylthio, heteroaralkoxy,
heteroaralkylthio, aralkoxy, aralkylthio,
aralkylamino, heterocyclo, heteroaryl, arylazo,
hydroxycarbonylalkoxy, alkoxycarbonylalkoxy,
alkanoyl, arylcarbonyl, aralkanoyl, alkanoyloxy,
10 aralkanoyloxy, hydroxyalkyl, hydroxyalkoxy,
alkylthio, alkoxyalkylthio, alkoxycarbonyl,
aryloxyalkoxyaryl, arylthioalkylthioaryl,
aryloxyalkylthioaryl, arylthioalkoxyaryl,
hydroxycarbonylalkoxy, hydroxycarbonylalkylthio,
15 alkoxycarbonylalkoxy, alkoxycarbonylalkylthio, amino,
wherein the amino nitrogen is (i) unsubstituted,
or (ii) substituted with one or two substituents
that are independently selected from the group
consisting of an alkyl, aryl, heteroaryl,
20 aralkyl, cycloalkyl, aralkoxycarbonyl,
alkoxycarbonyl, arylcarbonyl, aralkanoyl,
heteroarylcarbonyl, heteroaralkanoyl and an
alkanoyl group, or (iii) wherein the amino
nitrogen and two substituents attached thereto
25 form a 5- to 8-membered heterocyclo or
heteroaryl ring containing zero to two
additional heteroatoms that are nitrogen, oxygen
or sulfur and which ring itself is (a)
unsubstituted or (b) substituted with one or two
30 groups independently selected from the group
consisting of an aryl, alkyl, heteroaryl,
aralkyl, heteroaralkyl, hydroxy, alkoxy,
alkanoyl, cycloalkyl, heterocycloalkyl,

alkoxycarbonyl, hydroxyalkyl, trifluoromethyl,
benzofused heterocycloalkyl, hydroxyalkoxyalkyl,
aralkoxycarbonyl, hydroxycarbonyl,
aryloxycarbonyl, benzofused heterocycloalkoxy,
5 benzofused cycloalkylcarbonyl, heterocyclo-
alkylcarbonyl, and a cycloalkylcarbonyl group,
carbonylamino

wherein the carbonylamino nitrogen is (i)
unsubstituted, or (ii) is the reacted amine of
10 an amino acid, or (iii) substituted with one or
two radicals selected from the group consisting
of an alkyl, hydroxyalkyl, hydroxyheteroaralkyl,
cycloalkyl, aralkyl, trifluoromethylalkyl,
heterocycloalkyl, benzofused heterocycloalkyl,
15 benzofused heterocycloalkyl, benzofused
cycloalkyl, and an N,N-dialkylsubstituted
alkylamino-alkyl group, or (iv) the carboxamido
nitrogen and two substituents bonded thereto
together form a 5- to 8-membered heterocyclo,
20 heteroaryl or benzofused heterocycloalkyl ring
that is itself unsubstituted or substituted with
one or two radicals independently selected from
the group consisting of an alkyl,
alkoxycarbonyl, nitro, heterocycloalkyl,
25 hydroxy, hydroxycarbonyl, aryl, aralkyl,
heteroaralkyl and an amino group,

wherein the amino nitrogen is
(i) unsubstituted, or (ii) substituted with
one or two substituents that are
30 independently selected from the group
consisting of alkyl, aryl, and heteroaryl,
or (iii) wherein the amino nitrogen and two

substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring, and an aminoalkyl group wherein the aminoalkyl nitrogen is (i) unsubstituted, 5 or (ii) substituted with one or two substituents independently selected from the group consisting of an alkyl, aryl, aralkyl, cycloalkyl, aralkoxycarbonyl, alkoxycarbonyl, and an alkanoyl group, or (iii) wherein the aminoalkyl nitrogen and 10 two substituents attached thereto form a 5- to 8-membered heterocyclo or heteroaryl ring.

The term "aralkyl", alone or in combination, means an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl 15 radical as defined above, such as benzyl, 2-phenylethyl and the like.

The term "aralkoxycarbonyl", alone or in combination, means a radical of the formula aralkyl-O-C(O)- in which the term "aralkyl" has the 20 significance given above. An example of an aralkoxycarbonyl radical is benzyloxycarbonyl.

The term "aryloxy" means a radical of the formula aryl-O- in which the term aryl has the significance given above. The phenoxy radical is an 25 exemplary aryloxy radical.

The terms "heteroaralkyl" and "heteroaryloxy" mean radicals structurally similar to aralkyl and aryloxy that are formed from heteroaryl radicals. Exemplary radicals include 4-picolinyl and 30 2-pyrimidinoxy, respectively.

The terms "alkanoyl" or "alkylcarbonyl", alone or in combination, means an acyl radical

derived from an alkanecarboxylic acid, examples of which include formyl, acetyl, propionyl, butyryl, valeryl, 4-methylvaleryl, and the like.

The term "cycloalkylcarbonyl" means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropanecarbonyl, cyclohexanecarbonyl, adamantanecarbonyl, and the like, or from a benz-fused monocyclic cycloalkanecarboxylic acid that is optionally substituted by, for example, alkanoylamino, such as 1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl.

The terms "aralkanoyl" or "aralkylcarbonyl" mean an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl and the like.

The terms "aroyl" or "arylcarbonyl" means an acyl radical derived from an aromatic carboxylic acid. Examples of such radicals include aromatic carboxylic acids, an optionally substituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like.

The term "cycloalkylalkoxycarbonyl" means an acyl group of the formula cycloalkylalkyl-O-CO- wherein cycloalkylalkyl has the significance given

above. The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the significance given above. The term "heterocyclooxycarbonyl" means an acyl group
5 having the formula heterocyclo-O-CO- wherein heterocyclo is as defined above.

The term "heterocycloalkanoyl" is an acyl radical of the formula heterocyclo-substituted alkane carboxylic acid wherein heterocyclo has the
10 significance given above. The term "heterocycloalkoxycarbonyl" means an acyl radical of the formula heterocyclo-substituted alkane-O-CO- wherein heterocyclo has the significance given above. The term "heteroaryloxy carbonyl" means an acyl
15 radical represented by the formula heteroaryl-O-CO- wherein heteroaryl has the significance given above.

The term "aminocarbonyl" (carboxamide) alone or in combination, means an amino-substituted carbonyl (carbamoyl) group derived from an amine
20 reacted with a carboxylic acid wherein the amino (amido nitrogen) group is unsubstituted (-NH₂) or a substituted primary or secondary amino group containing one or two substituents selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like, as
25 recited. A hydroxamate is a N-hydroxycarboxamide.

The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkanecarboxylic acid wherein the amino group can be
30 a primary or secondary amino group containing substituents independently selected from hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like.

The term "halogen" means fluoride, chloride, bromide or iodide. The term "haloalkyl" means an alkyl radical having the significance as defined above wherein one or more hydrogens are replaced with a halogen. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like.

The term "perfluoroalkyl" means an alkyl group wherein each hydrogen has been replaced by a fluorine atom. Examples of such perfluoroalkyl groups, in addition to trifluoromethyl above, are perfluorobutyl, perfluoroisopropyl, perfluorododecyl and perfluorodecyl.

The term "perfluoroalkoxy" alone or in combination, means a perfluoroalkyl ether radical wherein the term perfluoroalkyl is as defined above. Examples of such perfluoroalkoxy groups, in addition to trifluoromethoxy ($\text{F}_3\text{C-O-}$), are perfluorobutoxy, perfluoroisopropoxy, perfluorododecoxy and perfluorodecoxy.

The term "perfluoroalkylthio" alone or in combination, means a perfluoroalkyl thioether radical wherein the term perfluoroalkyl is as defined above. Examples of such perfluoroalkylthio groups, in addition to trifluoromethylthio ($\text{F}_3\text{C-S-}$), are perfluorobutylthio, perfluoroisopropylthio, perfluorododecylthio and perfluorodecylthio.

The term "aromatic ring" in combinations such as substituted-aromatic ring sulfone or substituted-aromatic ring sulfoxide means aryl or heteroaryl as defined before.

The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include

5 metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal (Group Ia) salts, alkaline earth metal (Group IIa) salts and other physiological acceptable metal ions. Exemplary ions include

10 aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-

15 dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid,

20 phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic

25 acid, aspartic acid, glutamic acid, benzoic acid, and the like.

"M" utilized in the reaction schemes that follow represents a leaving group such as halogen, phosphate ester or sulfate ester.

Preparation of Useful Compounds

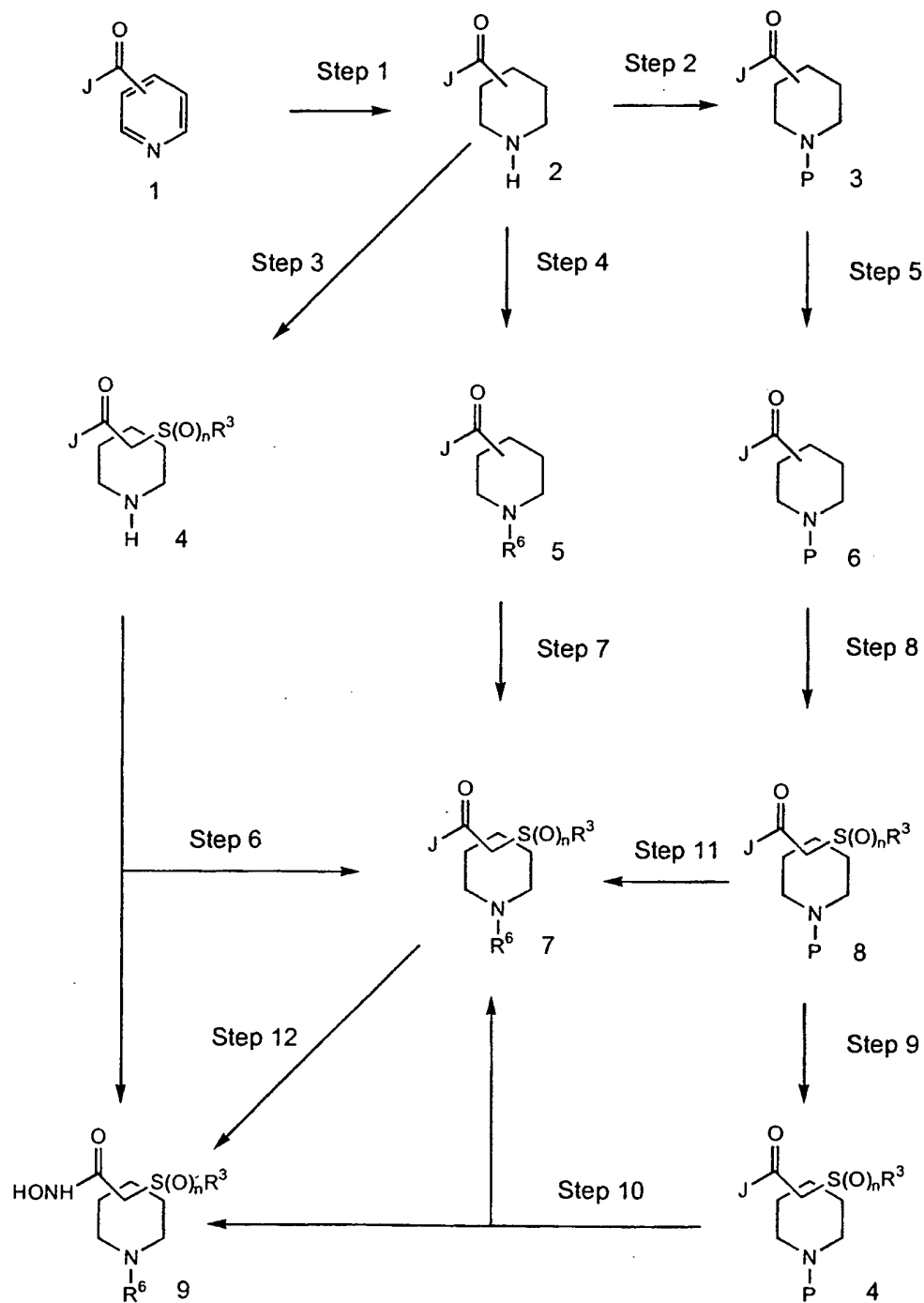
Schemes A through C and Schemes 1 through 19 hereinbelow illustrate chemical processes and transformations that can be useful for the preparation of compounds useful in this invention; i.e., compounds of formulas I, II, III, IV and V and similar cyclic inhibitors. In addition, the preparation of compounds of formula VI and formula VII is illustrated. Compounds of formula VI and formula VII can be used as intermediates in the preparation of the compounds of formulas I, II, III, IV and V or pro-drugs or MMP inhibitors.

In Schemes A through C, the symbol J independently represents R^{20} or other synthetically useful groups such as amides, acid chlorides, mixed anhydrides and the like. The n is 0, 1 or 2 and is preferred to be 1 or 2 in Scheme C. The n of these schemes corresponds to g in formulas VI and VII., and is zero, 1 or 2. The symbol m is 1 or 2. The symbol r is independently 1, 2 or 3. The symbol P represents a protecting group that can also be a member of the group R^6 . In Scheme A, for simplicity and clarity of illustration positional isomers are illustrated with a bond through the ring in standard fashion. Later Schemes typically only show one positional isomer but positional isomers are represented by these structures and reactions in a manner consistent with Formula I, II, III, IV, V, VI, VII above. Similarly, the symbol B represents O, S, SO , SO_2 and NR^6 . The symbols C and C' independently are electrophilic groups or groups capable of participating in a condensation reaction. Here to it

should be noted that the six-membered ring is shown for illustrative purposes but the procedures and/or reagents are applicable to and represent combinations the permit the preparation of 5- to 8-membered rings.

5 The structures in Schemes 1 through 19 are also shown with compounds that represent the other compounds of this invention. The aromatic ring in Scheme C is aryl and heteroaryl. The moieties of -A-
10 R-E-Y are as defined before. Reactions illustrated involving a spiroheterocyclic nitrogen atom may not be applicable to those compounds with sulfur or oxygen.

Scheme A



Scheme A shows in step 1 the reduction of a heteraryl compound to a carboxyl derivative.

Generally, the first product is a hydrogen-containing amine heterocycle when the starting material is

5 aromatic or an R^6 -containing heterocycle when a partially unsaturated heterocycle is the starting material.

Compound 2 can be treated in several ways depending on the needs of the chemist. In Step 2,
10 the nitrogen can be protected by preparing, for example, a carbobenzoxy (Z) or tert-butoxycarbonyl derivative. Such acylations can be carried out by methods well known in the art, especially the art of amino acid and peptide synthesis. The process of
15 acylation with activated carboxyl group- or activated sulfonyl group-containing reagents to prepare contemplated compounds is carried out in the same manner. Examples of such acylating groups are carbonyl azides, halides, anhydrides, mixed
20 anhydrides, carbodiimide derivatives or other less traditional activated ester groups such as the hydroxybenzotriazole derivative. These acylations can be run in the presence of base including mild bases such as triethylamine or N-ethylmorpholine if
25 desired. The preparation of some activated ester reagents and their use to prepare other compounds useful in this invention is discussed below. It should be recalled that the groups constituting P and serving as a selectively removable protecting group
30 can also be included as part of the group R^6 .

Step 4 of Scheme A shows the alkylation or acylation of Compound 2 to produce compound 5. The

process of acylation and alkylation are as discussed herein. In Step 5, the group J can be changed if desired. An example of such a change is exchange of an ester for a THP-protected hydroxamate conversion of a THP-protected hydroxamate into a hydroxamate or conversion of an acid into a protected hydroxamate or the like.

Steps 3, 7 and 8 show the preparation of sulfur-containing derivatives of the contemplated compounds or intermediates to those compounds. The starting material for the above steps (e.g., compounds 2, 5 and 6) can be treated with a base to deprotonate the carbon alpha to the carbonyl function. This anion can be reacted with a sulfur electrophile to produce a sulfone, sulfoxide or sulfide. Such electrophiles can be of the form of, for example, $R^{24}S-SR^{24}$, $R^{24}SO_2Cl$, $R^{24}SCl$, $R^{24}SOCl$, $R^{24}S(O)-SR^{24}$ and the like where R^{24} is as defined before or is an aryl or heteroaryl sulfur-containing material containing a coupling substituent, $R^{3'}$, that can be used to prepare one of the R^{24} -containing groups. Preparation of the anion requires a base and a strong base may be required such as one of the metal amides, hydrides or alkyls discussed herein. The solvents are nonprotic, and dipolar aprotic solvents are preferred along with an inert atmosphere. Subsequent schemes usually utilize R^3 for the R^{24} group for ease of illustration.

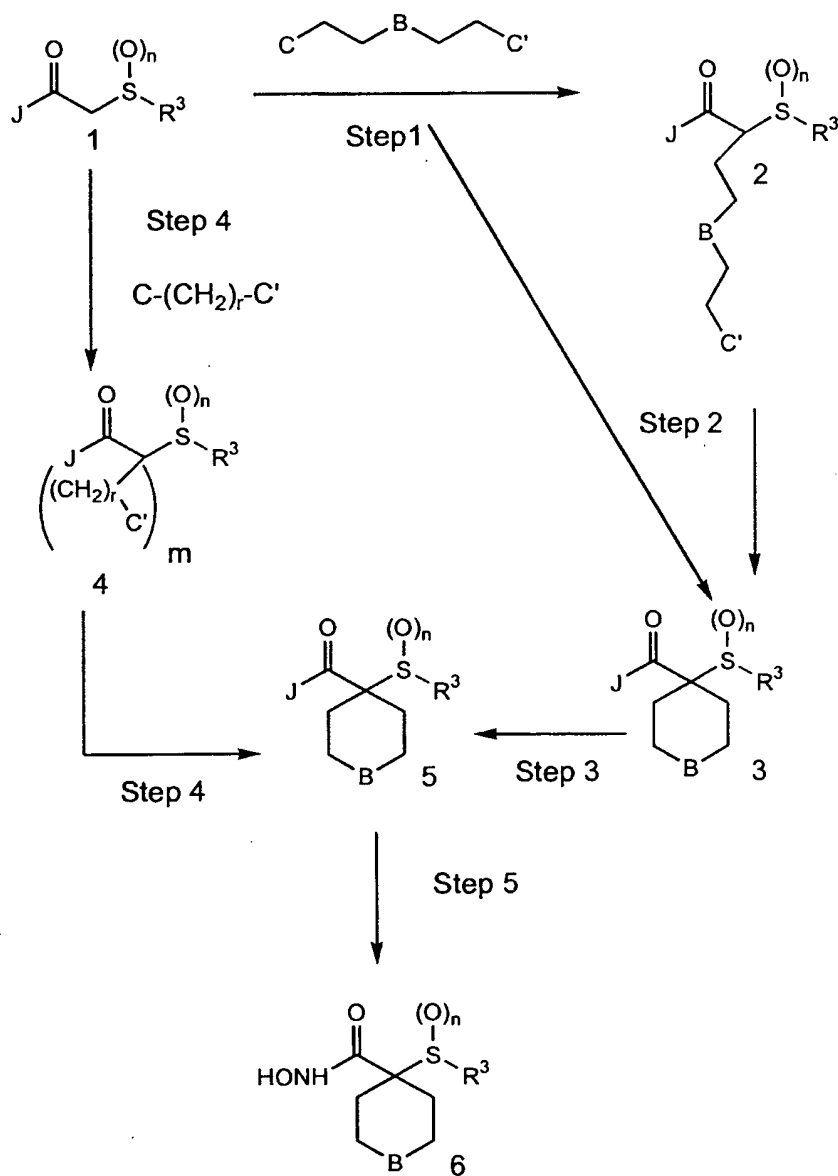
It should be noted that these processes produce sulfides (thio ethers), sulfoxides or sulfones depending on starting material. In

addition, the sulfides can be oxidized to sulfoxides or sulfones, and the sulfoxides can be oxidized to their corresponding sulfone derivatives. The choice of position in the synthetic sequence to change the oxidation state of sulfur as well as the decision to change oxidation state is under the control of the chemist skilled in the art. Methods of oxidizing sulfur are discussed hereinbelow.

Scheme A, Steps 6, 9, 10 and 12

independently illustrate the interconversion of groups within J. Examples of such interconversions include exchange of an ester for hydroxamic acid or hydroxamic acid derivative, conversion of a carboxylic acid into an activated carbonyl derivative or into a hydroxamic acid or hydroxamic acid derivative(pro-drug or protected derivative), or removal of a protecting group from a hydroxamate derivative. The preparation of activated carbonyl compounds their reaction with nucleophiles such as hydroxamic acid, protected hydroxamates or hydroxamic acid pro-drugs is discussed below as is the conversion of protected hydroxamic acid derivatives into hydroxamic acids. The preparation of, for example, hydroxybenzotriazole/carbodiimide, derived products is discussed herein. The preparation or hydrolysis of esters, amides, amide derivatives, acid chlorides, acid anhydrides, mixed anhydrides and the like are synthetic methods very well known in the art, and are not discussed in detail herein. Step 6 illustrates the conversion of compound 4 into compound 9, without first being converted into compound 7.

Scheme B



5 Scheme B illustrates an alternate method of preparing contemplated compounds. The reagent shown above the arrow in Step 1 is a reagent with two

active groups in addition to the heteroatoms (B) noted before. Here again, the particular reagent illustrated was selected to permit a clear illustration of the reaction, but it is also intended to represent reagents that permit the preparation of the heteroatom position, and 5-, 7- and 8-membered ring size compounds. These reagents are readily selected by those skilled in the art.

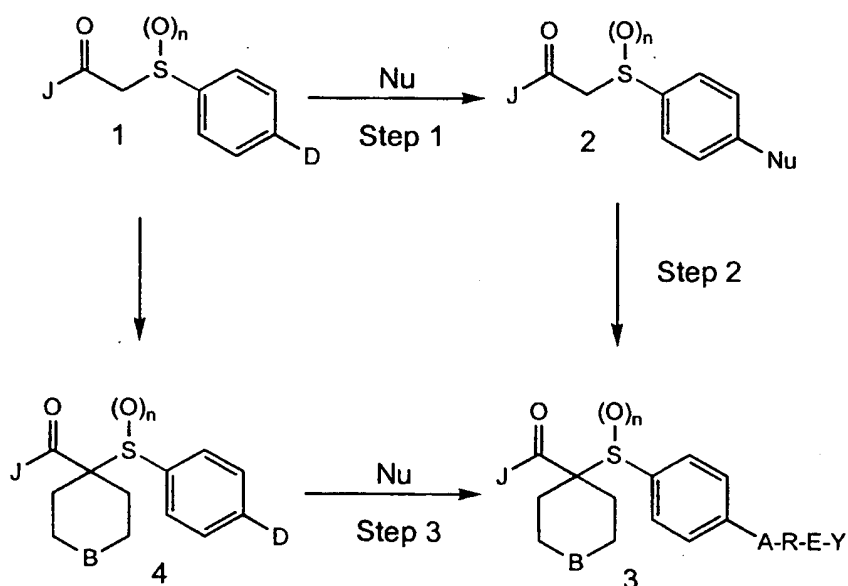
C and C' in this Step 1 reagent are independently an electrophile or a group convertible into an electrophile. Such groups include halides, sulfonic acid esters, epoxides, thioepoxides, hydroxyl groups, and the like. This reagent is reacted with a nucleophilic anion of a sulfur containing carbonyl compound such as compound 1. The anion is formed by deprotonation of compound 1 and examples of bases suitable for such a deprotonation are discussed below. Treatment with the above electrophilic reagent is carried out under alkylating conditions well known in the art and discussed herein. The product of this reaction can be either Compound 2 or Compound 3; i.e., the reaction can be carried out as a pot or two step process as required.

Step 3 illustrates the interconversion of J groups if desired as discussed above for Scheme A. Step 4 uses reagent where C, for example, represents a nucleophile as discussed above and C' represents an electrophile or a nucleophile such as hydroxyl, thiol or R⁶-amino. It is noted that C' can be, independently, a nucleophile or an electrophile when m is 2; i.e., the C' groups are not required to be the same when m is 2. When m is 2, treatment with a second mole of base provides the skilled chemist an

alternative preparation of Compound 5. When C' is hydroxyl, thiol, or R⁶-amino and m is 2, the person skilled in the art can condense Compound 4 with, for example, an aldehyde or ketone, under reductive conditions or with subsequent reduction to form a contemplated compound. As above, the compound where m is 2 can be made in one step (one pot process) or two steps, thus permitting the chemist the choice of having the reagent(s) be the same (one pot) or different (two step).

Scheme B also illustrates the interconversions of the groups within J, the oxidation state of the sulfur and groups on nitrogen; i.e., R⁶ groups, to provide the contemplated compounds. These methods and processes are discussed above for the reactions of Scheme A.

Scheme C



Scheme C illustrates the nucleophilic displacement of a group D as defined herein. This reaction is carried out in a similar manner to the displacement reactions discussed herein. The choice of oxidation state of the sulfur is made by the person skilled in the art, but sulfoxide or sulfone groups are preferred, and the sulfone is most preferred. The displacement can be carried out either before or after the methylene next to the carbonyl group is reacted to form a spiro heterocyclic group.

Steps 1, 2 and 3 also illustrate that although the nucleophilic displacement can be carried out with one nucleophile (Nu), the product of this reaction can be modified by methods well known in the art and as shown herein to provide the group -A-R-E-Y as defined hereinbefore.

A non-limiting illustration of such a process is provided when D is fluoride. The fluoride leaving group can be directly displaced with the anion of 4-trifluoromethylphenol, 4-trifluoromethoxyphenol, 4-trifluoromethylthiophenol and the like to provide a contemplated compound. This is a one pot process from Compound 4. Other compounds included in -A-R-E-Y can be prepared by displacing the fluoride leaving group with ammonia to provide an amine, which can then be acylated by methods discussed wherein with, for example, 4-trifluoromethylbenzoyl chloride, to form another contemplated product compound.

The R⁶ function can be changed and/or further modified in compounds or at steps in the Schemes as desired or required by the person skilled in the art to prepare the contemplated compounds.

5 Interconversion of dual purpose functional groups such as short or long term protecting groups into other R⁶ groups has been mentioned. Many other routine and/or useful conversions, including the preparation of synthetic intermediates, are very well
10 known in the art. A few non-limiting examples of such conversions or reactions include: reductions; nucleophilic displacement/substitution reactions; exchange or preparation of carboxylic or sulfonic acids, amides, esters, acid halides, mixed anhydrides
15 and the like; electrophilic displacement/substitution reactions; oxidations; ring/chain conversions, ring opening reactions, condensation reactions including those involving sulfonyl or carbonyl groups and/or carbon-hydrogen bonds influenced by either or both of
20 those groups. The selection of preparative methods or conversion methods of the contemplated compounds and the order of the reaction(s) is made by the skilled person. It is expected that should a particular sequence or method prove to be undesirable
25 that an alternative will be selected and used. Included is the choice of preparing/adding the groups in a single step using a convergent inhibitor strategy or preparing the final R⁶ group following a stepwise strategy.

30 Thus, in general, the choices of starting material and reaction conditions can vary as is well known to those skilled in the art. Usually, no

single set of conditions is limiting because variations can be applied as required. Conditions are also selected as desired to suit a specific purpose such as small scale preparations or large
5 scale preparations. In either case, the use of less safe or less environmentally sound materials or reagents is usually be minimized. Examples of such materials are diazomethane, diethyl ether, heavy metal salts, dimethyl sulfide, chloroform, benzene
10 and the like.

These reactions can be carried out under a dry inert atmosphere such a nitrogen or argon if desired. Selected reactions known to those skilled in the art, can be carried out under a dry atmosphere
15 such as dry air whereas other synthetic steps, for example, aqueous acid or base ester or amide hydrolysis, can be carried out under laboratory air. In addition, some processes of these syntheses can be carried out in a pressure apparatus at pressures
20 above, equal to or below atmospheric pressure. The use of such an apparatus aids in the control of gaseous reagents such as hydrogen, ammonia, trimethylamine, methylamine, oxygen and the like, and can also help prevent the leakage of air or humidity
25 into a reaction in progress. This discussion is not intended to be exhaustive as it is readily noted that additional or alternative methods, conditions, reactions or systems can be identified and used by a chemist of ordinary skill.

30 The illustrated reactions are usually carried out at a temperature of between -25°C to solvent reflux under an inert atmosphere such as nitrogen or argon. The solvent or solvent mixture

can vary widely depending upon reagents and other conditions and can include polar or dipolar aprotic solvents as listed or mixtures of these solvents. Reactions can be carried out at lower temperatures
5 such as dry ice/acetone or liquid nitrogen temperature if desired to carry out such reactions as metalations or anion formations using strong bases.

In some cases, amines such as triethylamine, pyridine or other non-reactive bases
10 can serve as reagents and/or solvents and/or co-solvents. In some instances, in these reactions and other reactions in these Schemes, protecting groups can be used to maintain or retain groups in other parts of a molecule(s) at locations that is(are) not
15 desired reactive centers. Examples of such groups that the skilled person can maintain or retain include, amines, other hydroxyls, thiols, acids and the like. Such protecting groups can include acyl groups, arylalkyl groups, carbamoyl groups, ethers,
20 alkoxyalkyl ethers, cycloalkyloxy ethers, arylalkyl groups, silyl groups including trisubstituted silyl groups, ester groups and the like. Examples of such protecting groups include acetyl, trifluoroacetyl, tetrahydropyran (THP), benzyl, tert-butoxy carbonyl
25 (BOC or TBOC), benzyloxycarbonyl (Z or CBZ), tert-butyltrimethylsilyl (TBDMS) or methoxyethoxymethylene (MEM) groups. The preparation of such protected compounds as well as their removal is well known in the art. The protecting groups can also be used as
30 substituents in the contemplated compounds whose utility is as a drug rather than as a synthetic intermediate.

Many reactions or processes involve bases that can act as reactants, reagents, deprotonating agents, acid scavengers, salt forming reagents, solvents, co-solvents and the like. Bases that can be used include, for example, metal hydroxides such as sodium, potassium, lithium, cesium or magnesium hydroxide, oxides such as those of sodium, potassium, lithium, calcium or magnesium, metal carbonates such as those of sodium, potassium, lithium, cesium, calcium or magnesium, metal bicarbonates such as sodium bicarbonate or potassium bicarbonate, primary (I°), secondary (II°) or tertiary (III°) organic amines such as alkyl amines, arylalkyl amines, alkylarylalkyl amines, heterocyclic amines or heteroaryl amines, ammonium hydroxides or quaternary ammonium hydroxides. As non-limiting examples, such amines can include triethylamine, trimethylamine, diisopropylamine, methyldiisopropylamine, diazabicyclononane, tribenzylamine, dimethylbenzylamine, morpholine, N-methylmorpholine, N,N'-dimethylpiperazine, N-ethylpiperidine, 1,1,5,5-tetramethylpiperidine, dimethylaminopyridine, pyridine, quinoline, tetramethylethylenediamine, and the like. Non-limiting examples of ammonium hydroxides, usually made from amines and water, can include ammonium hydroxide, triethylammonium hydroxide, trimethylammonium hydroxide, methyldiisopropylammonium hydroxide, tribenzylammonium hydroxide, dimethylbenzylammonium hydroxide, morpholinium hydroxide, N-methylmorpholinium hydroxide, N,N'-dimethylpiperazinium hydroxide, N-ethylpiperidinium hydroxide, and the like. As non-limiting examples,

quaternary ammonium hydroxides can include tetraethylammonium hydroxide, tetramethylammonium hydroxide, dimethyldiisopropyl-ammonium hydroxide, benzylmethyldiisopropylammonium hydroxide, 5 methyldiazabicyclononylammonium hydroxide, methyltribenzylammonium hydroxide, N,N-dimethyl-morpholiniumhydroxide, N,N,N',N'-tetramethylpiperazinium hydroxide, and N-ethyl-N'-hexylpiperidinium hydroxide and the like.

10 Metal hydrides, amides or alcoholates such as calcium hydride, sodium hydride, potassium hydride, lithium hydride, aluminum hydride, diisobutylaluminum hydride (DIBAL) sodium methoxide, potassium tert-butoxide, calcium ethoxide, magnesium 15 ethoxide, sodium amide, potassium diisopropyl amide and the like can also be suitable reagents.

Organometallic deprotonating agents such as alkyl or aryl lithium reagents such as methyl lithium, phenyl lithium, tert-butyl lithium, lithium acetylide or 20 butyl lithium, Grignard reagents such as methylmagnesium bromide or methymagnesium chloride, organocadmium reagents such as dimethylcadmium and the like can also serve as bases for causing salt formation or catalyzing the reaction. Quaternary 25 ammonium hydroxides or mixed salts are also useful for aiding phase transfer couplings or serving as phase transfer reagents. Pharmaceutically acceptable bases can be reacted with acids to form contemplated pharmaceutically acceptable salts. It should also be 30 noted that optically active bases can be used to make optically active salts which can be used for optical resolutions.

Generally, reaction media can comprise a single solvent, mixed solvents of the same or different classes or serve as a reagent in a single or mixed solvent system. The solvents can be protic, non-protic or dipolar aprotic. Non-limiting examples of protic solvents include water, methanol (MeOH), denatured or pure 95% or absolute ethanol, isopropanol and the like. Typical non-protic solvents include acetone, tetrahydrofuran (THF), dioxane, diethyl ether, tert-butylmethyl ether (TBME), aromatics such as xylene, toluene, or benzene, ethyl acetate, methyl acetate, butyl acetate, trichloroethane, methylene chloride, ethylenedichloride (EDC), hexane, heptane, isooctane, cyclohexane and the like. Dipolar aprotic solvents include compounds such as dimethylformamide (DMF), dimethylacetamide (DMAc), acetonitrile, DMSO, hexamethylphosphorus triamide (HMPA), nitromethane, tetramethylurea, N-methylpyrrolidone and the like. Non-limiting examples of reagents that can be used as solvents or as part of a mixed solvent system include organic or inorganic mono- or multi-protic acids or bases such as hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, formic acid, citric acid, succinic acid, triethylamine, morpholine, N-methylmorpholine, piperidine, pyrazine, piperazine, pyridine, potassium hydroxide, sodium hydroxide, alcohols or amines for making esters or amides or thiols for making contemplated products and the like.

The preparation of compounds contemplated herein can require the oxidation of nitrogen or sulfur to N-oxide derivatives or sulfoxides or sulfones. Reagents for this process can include, in

a non-limiting example, peroxymonosulfate (OXONE®), hydrogen peroxide, meta-chloroperbenzoic acid, perbenzoic acid, peracetic acid, perlactic acid, tert-butyl peroxide, tert-butyl hypochlorite, sodium
5 hypochlorite, hypochlorous acid, sodium meta-periodate, periodic acid and the like with the weaker agents being most useful for the preparation of sulfones and sulfoxides. Protic, non-protic, dipolar aprotic solvents, either pure or mixed, can be
10 chosen, for example, methanol/water.

The oxidation can be carried out at temperature of about -78° to about 50° degrees Centigrade, and normally selected from a range -10°C to about 40°C. Sulfoxides are best prepared using
15 one equivalent of oxidizing agent. It can be desirable in the case of more active oxidizing agents, but not required, that the reactions be carried out under an inert gas atmosphere with or without degassed solvents. It should be noted that
20 the oxidation of sulfides to sulfones can be carried out in one step or two steps via the sulfoxide as desired by the chemist.

Reduction is a well known process in the art with a useful method being hydrogenation. In
25 such cases (catalytic reduction), there can be a metal catalyst such as Rh, Pd, Pt, Ni or the like with or without an additional support such as carbon, barium carbonate and the like. Solvents can be protic or non-protic pure solvents or mixed solvents
30 as required. The reductions can be carried out at atmospheric pressure to a pressure of multiple atmospheres with atmospheric pressure to about 40 pounds per square inch (psi) preferred or very high

pressures in special hydrogenation equipment well known in the art.

Reductive alkylation of amines or active methylene compounds is also a useful method of preparing compounds. Such alkylations can be carried out under reductive hydrogenation conditions as presented above using, for example, aldehydes or ketones. Hydride transfer reagents such as sodium cyanoborohydride, aluminum hydride, lithium aluminumhydride, borane, sodium borohydride, di-isobutylaluminum hydride and the like are also useful as reagents for reductive alkylation. Acyl groups can be reduced in a similar manner to produce substituted amines.

Alternative methods of alkylating carbon or nitrogen are direct alkylation. Such an alkylation, as is well known in the art, can be carried by treatment of an activated carbon containing at least one hydrogen with base to form the corresponding anion, adding an electrophilic reagent and permitting the SN2 reaction to proceed. An amine to be alkylated is treated similarly except that deprotonation may not be required. Electrophiles include halogen derivatives, sulfonate esters, epoxides and the like.

Bases and solvents for alkylation reactions are those discussed above. Preferred are bases that are hindered such that competition with the electrophile is minimized. Additional preferred bases are metal hydrides, amide anions or organometallic bases such as n-butyl lithium. The solvents, solvent mixtures or solvent/reagent mixtures discussed are satisfactory but non-protic or

dipolar aprotic solvents such as acetone, acetonitrile, DMF and the like are examples of preferred classes.

Acids are used in many reactions during various syntheses. For example, removal of the THP protecting group to produce the hydroxamic acid. The acid can be a mono-, di- or tri-protic organic or inorganic acid. Examples of acids include hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, formic acid, citric acid, succinic acid, hydrobromic acid, hydrofluoric acid, carbonic acid, phosphorus acid, p-toluene sulfonic acid, trifluoromethane sulfonic acid, trifluoroacetic acid, difluoroacetic acid, benzoic acid, methane sulfonic acid, benzene sulfonic acid, 2,6-dimethylbenzene sulfonic acid, trichloroacetic acid, nitrobenzoic acid, dinitrobenzoic acid, trinitrobenzoic acid, and the like. They can also be Lewis acids such as aluminum chloride, borontrifluoride, antimony pentafluoride and the like. Acids in a protic can also be used to hydrolyze esters, amides and the like as well as catalyze exchange reactions.

Conversion of a carboxylic acid protected as an ester or amide into a hydroxamic acid or hydroxamic acid derivative such as an O-arylalkylether or O-cycloalkoxyalkylether group is useful. In the case where hydroxylamine is used, treatment of an ester or amide with one or more equivalents of hydroxylamine hydrochloride at room temperature or above in a solvent or solvents, usually protic or partially protic, such as those listed above can provide a hydroxamic acid directly. This exchange process can be further catalyzed by the

addition of additional acid. Alternatively, a base such as a salt of an alcohol used as a solvent, for example, sodium methoxide in methanol, can be used to form hydroxylamine from hydroxylamine hydrochloride in situ which can exchange with an ester or amide. As mentioned above, exchange can be carried out with a protected hydroxyl amine such as tetrahydropyranylhdroxyamine (THPONH₂), benzylhydroxylamine (BnONH₂), and the like in which case compounds such as shown in Schemes A, B and C that are tetrahydropyranyl (THP) or benzyl (Bn) hydroxamic acid derivatives are the products. Removal of the protecting groups when desired, for example, following further transformations in another part of the molecule or following storage, is accomplished by standard methods well known in the art such as acid hydrolysis of the THP group as discussed above or reductive removal of the benzyl group with hydrogen and a metal catalyst such as palladium, platinum, palladium on carbon or nickel.

In the case where R²⁰ is hydroxyl; i.e., where the intermediate is a carboxylic acid, standard coupling reactions can be used. For example, the acid can be converted into an acid chloride, mixed anhydride or activated ester such as hydroxybenzotriazole and treated with hydroxylamine or a protected hydroxylamine in the presence of a non-competitive base to the nitrogen acylated compound. This is the same product as discussed above. Couplings of this nature are well known in the art and especially the art related to peptide and amino acid chemistry.

An amide of this invention, whether used as a drug or as a protecting group, is prepared by treatment of an acid halide, anhydride, mixed anhydride or active ester with a primary amine, secondary amine or ammonia, or their equivalent. These standard coupling reactions are well known in the art and are discussed elsewhere herein. An alternative method of preparation of amides is by the exchange of, for example, an alkoxycarbonyl (ester) or aminecarbonyl (amide) group for an amine or different amine as required. Ester exchange processes are especially useful when less hindered amines, including ammonia, are used to make the corresponding amides of this invention.

Further, amides can be prepared from hydroxamic acids or protected hydroxamic acid compounds by catalytic reductions or *in vivo* or *in vitro* enzymatic processes. For example, catalytic reduction of O-benzylhydroxamic acid compounds is known to produce varying ratios of amide and hydroxamic acid depending upon the catalyst used as well as other reaction conditions such as solvent, temperature, hydrogen gas pressure and the like.

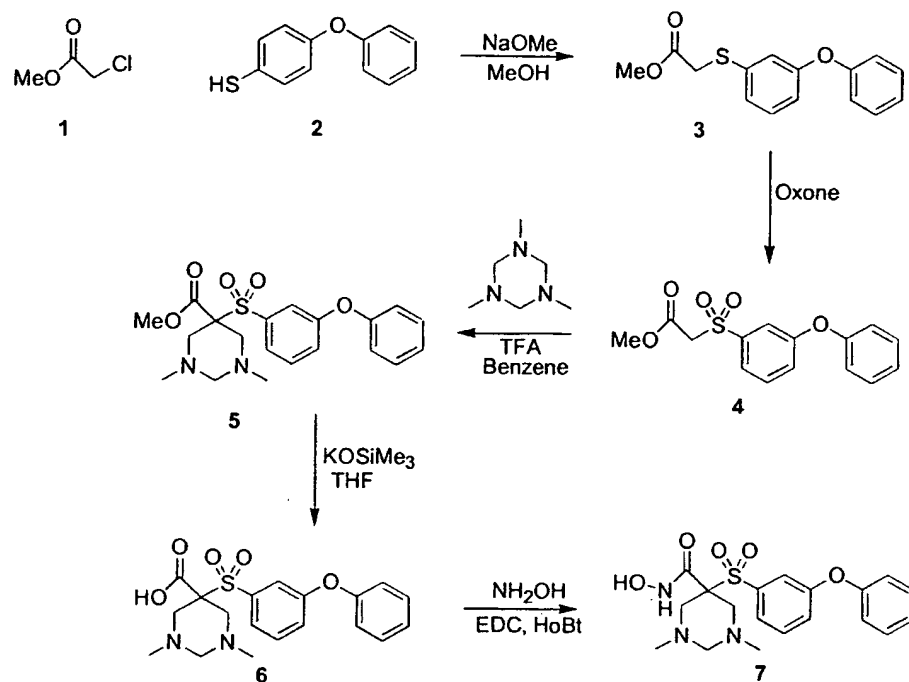
Compounds contemplated herein can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers, enantiomers, diastereoisomers, as well as in the form of racemic or nonracemic mixtures. A compound can also exist in other isomeric forms such as ortho, meta and para isomers, cis and trans isomers, syn and anti isomers, E and Z isomers, tautomeric isomers, alpha and beta isomers, axial and equatorial isomers and isomers due to hindered rotation. An isomer can

exist in equilibrium with another isomer in a mammal or a test system. Such a compound can also exist as an isomeric equilibrium system with a solvent or water, for example, as a hydrated ketone or aldehyde, as is well known in the art. All isomers are included as compounds of this invention.

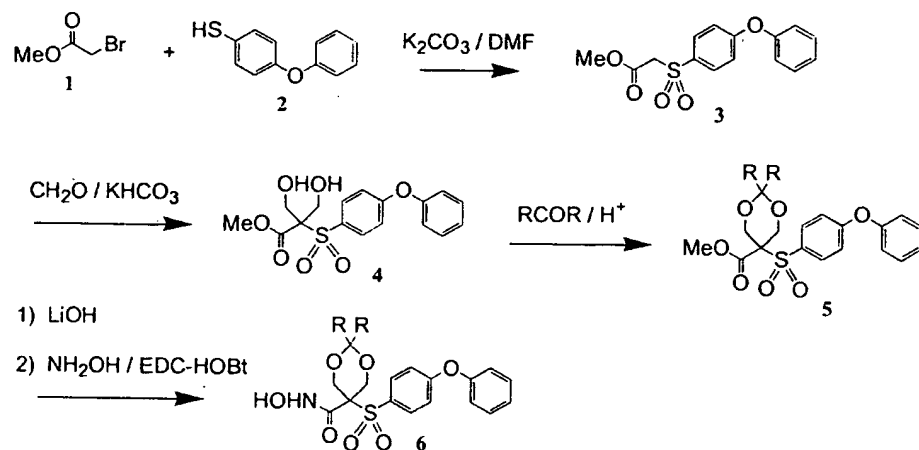
The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, are applicable to the preparation of the corresponding compounds that are contemplated.

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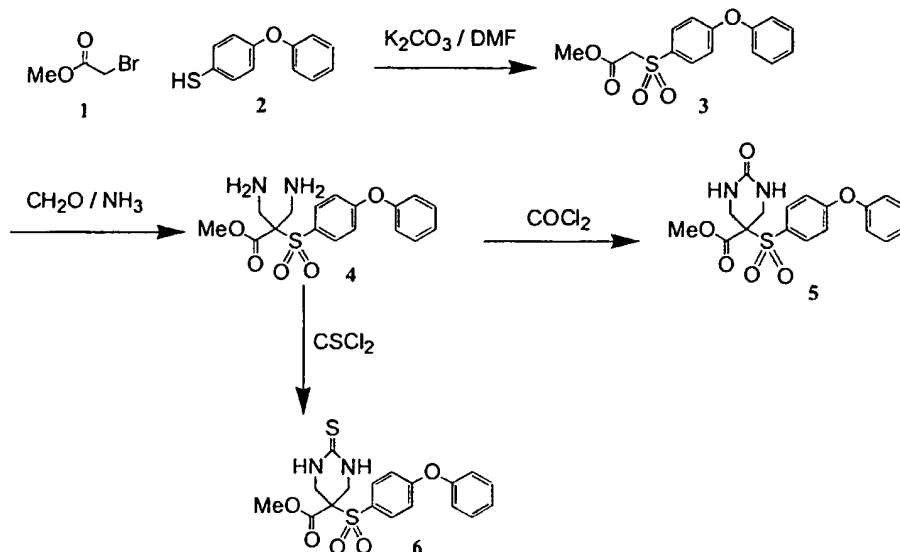
Scheme 1



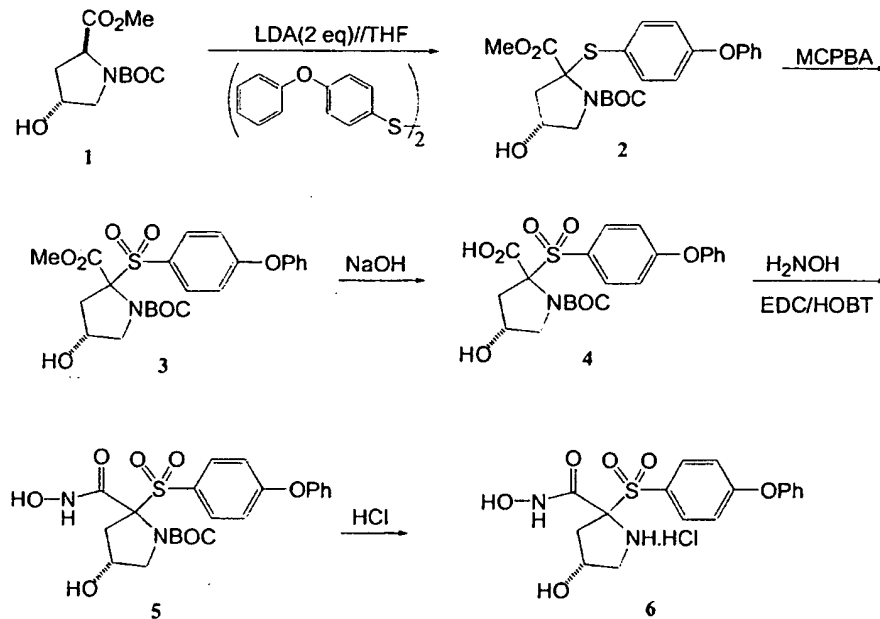
Scheme 2



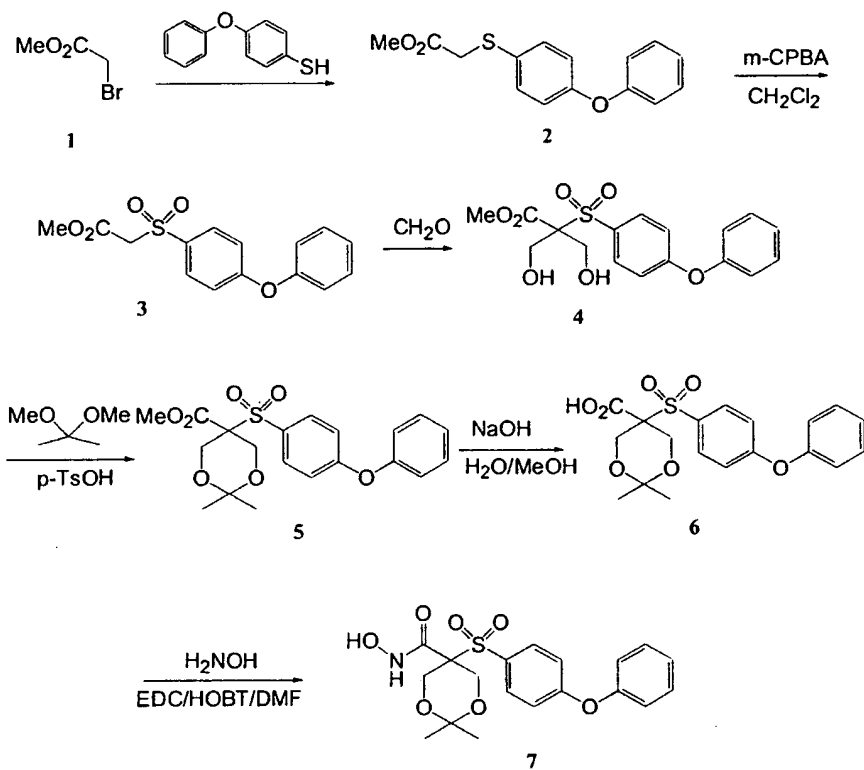
Scheme 3



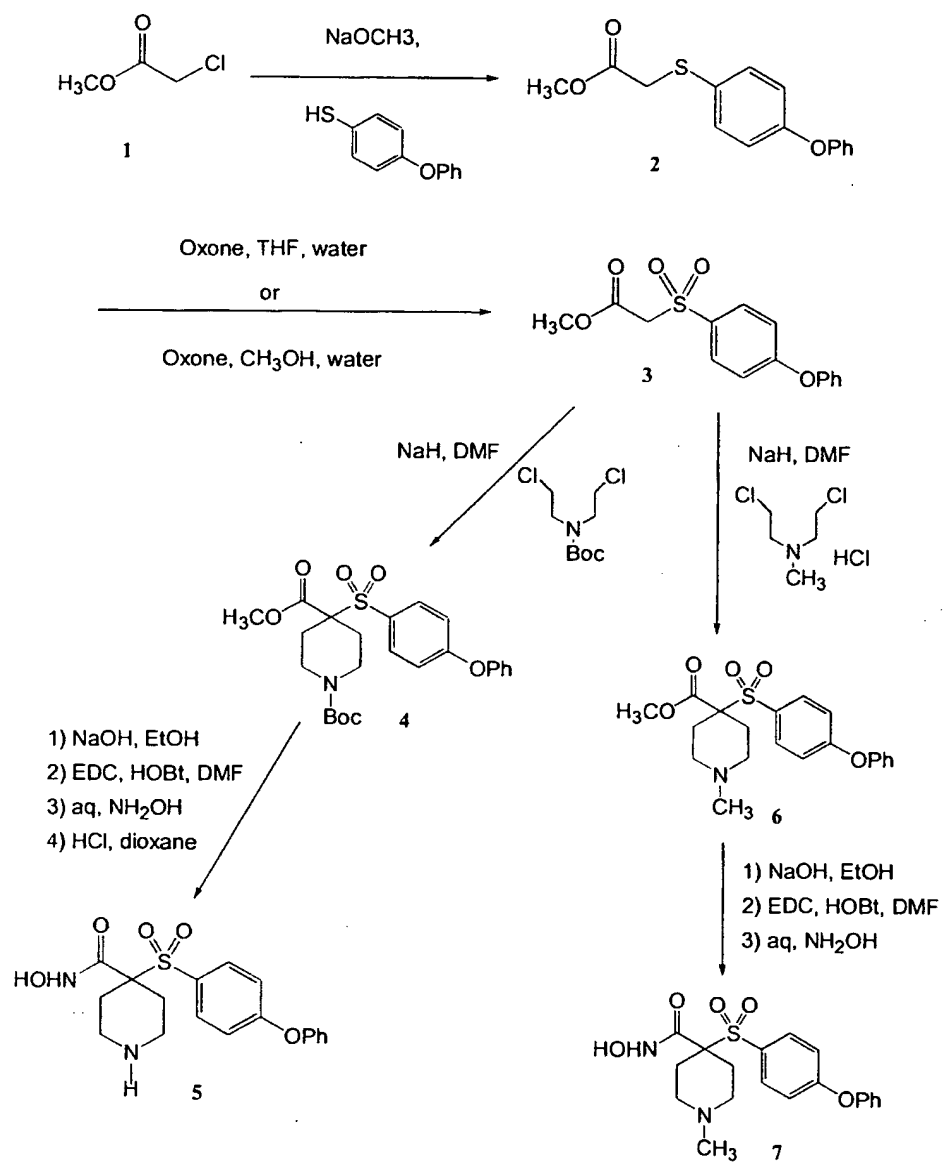
Scheme 4



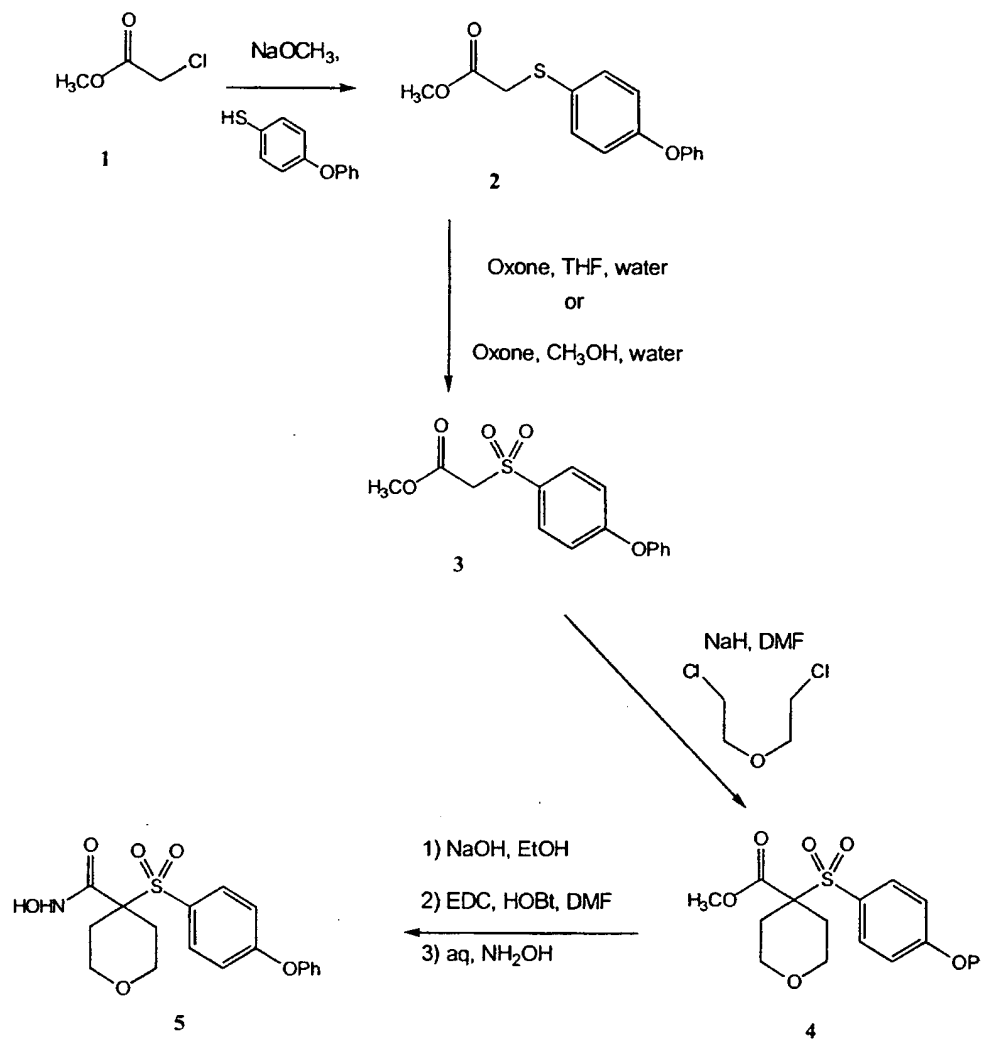
Scheme 5



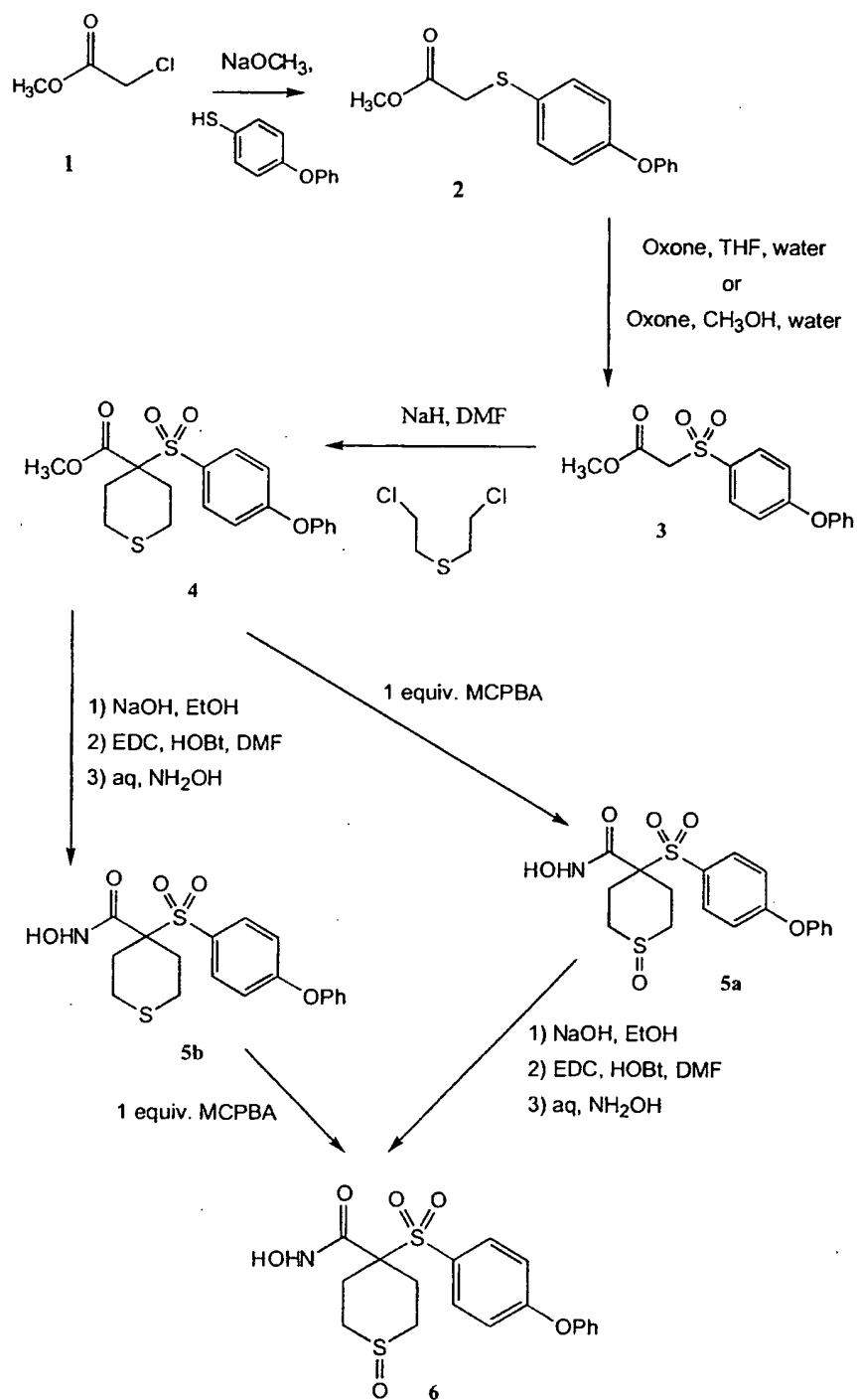
Scheme 6



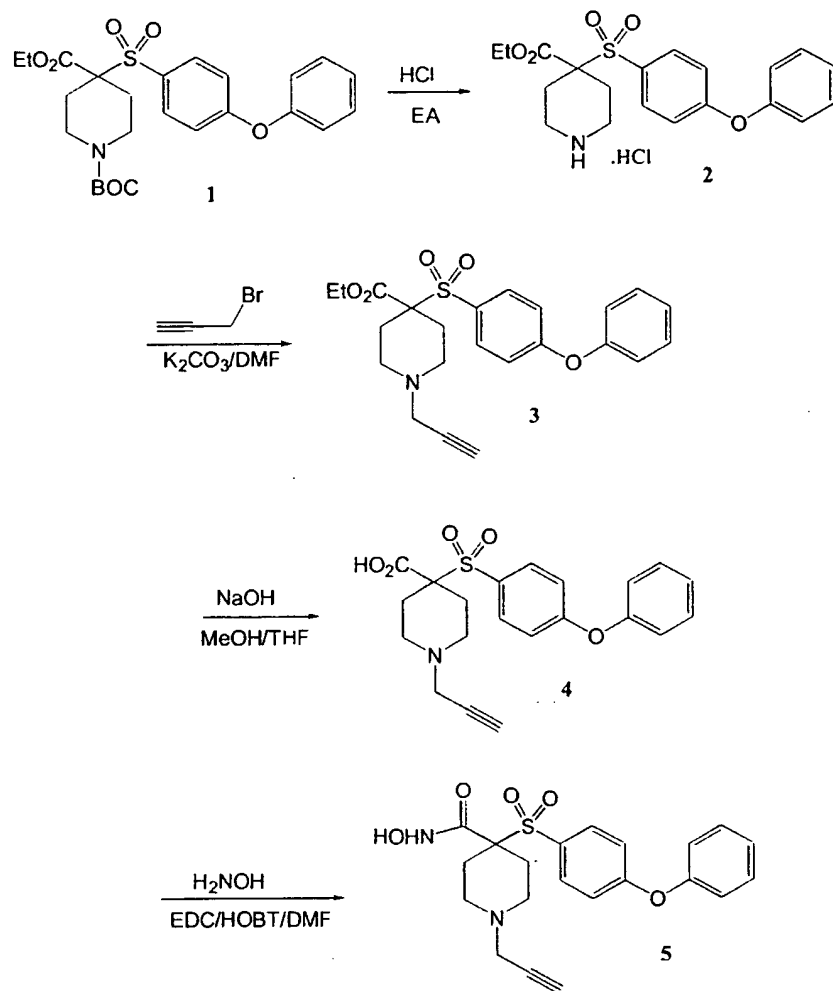
Scheme 7



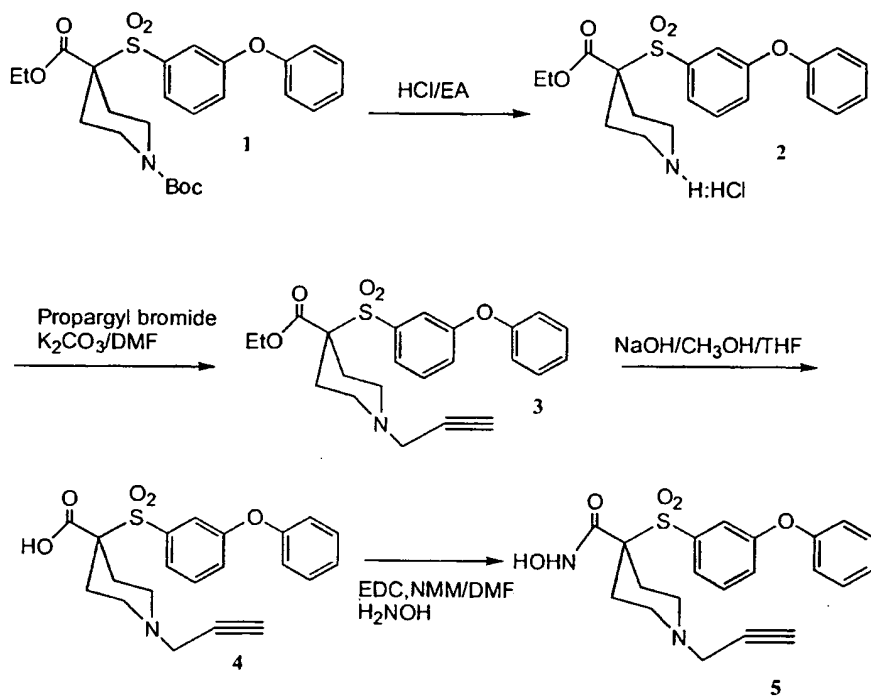
Scheme 8



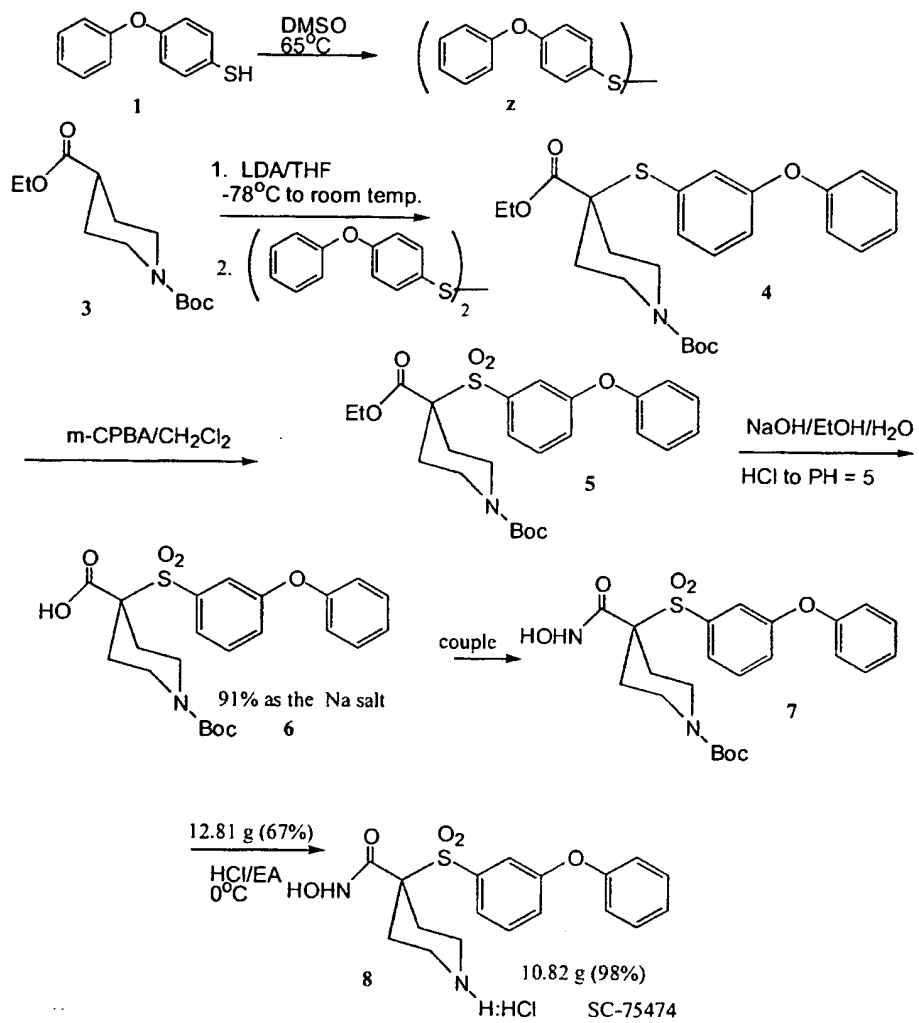
Scheme 9



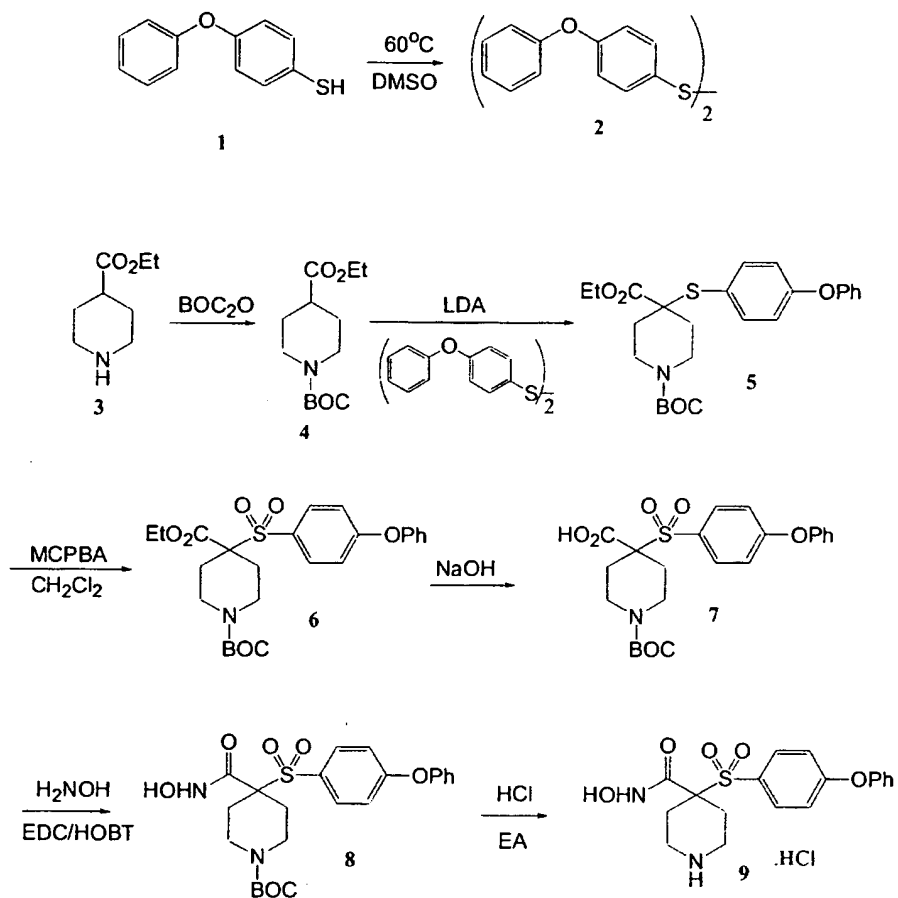
Scheme 10



Scheme 11

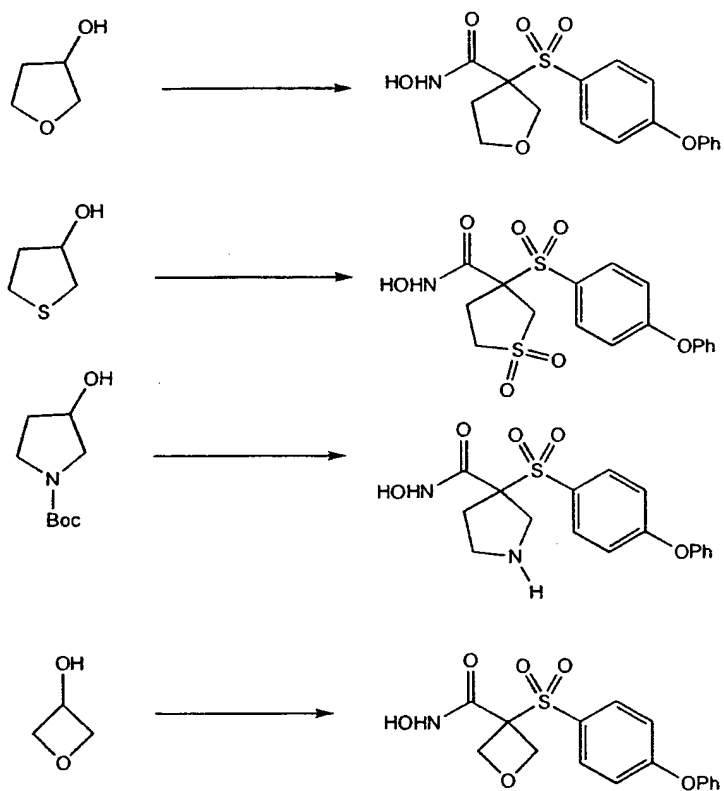


Scheme 12

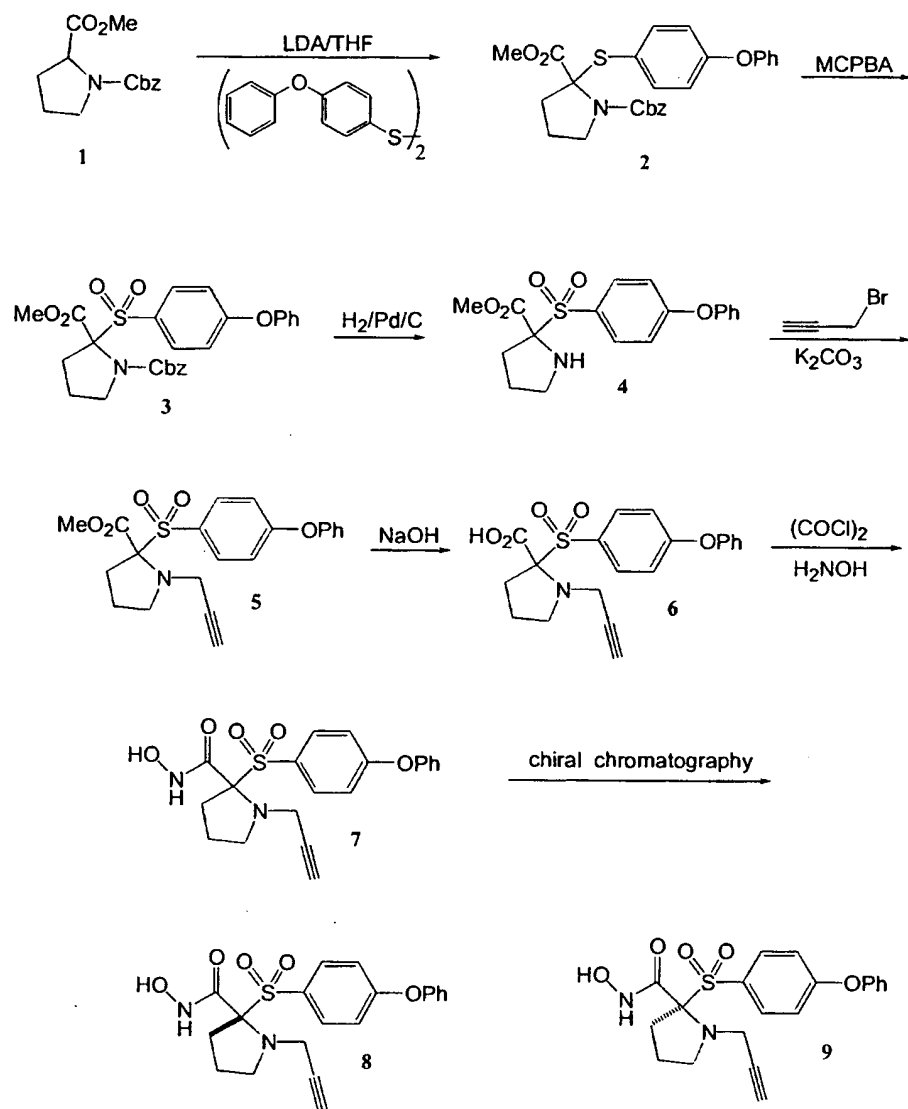


Scheme 13

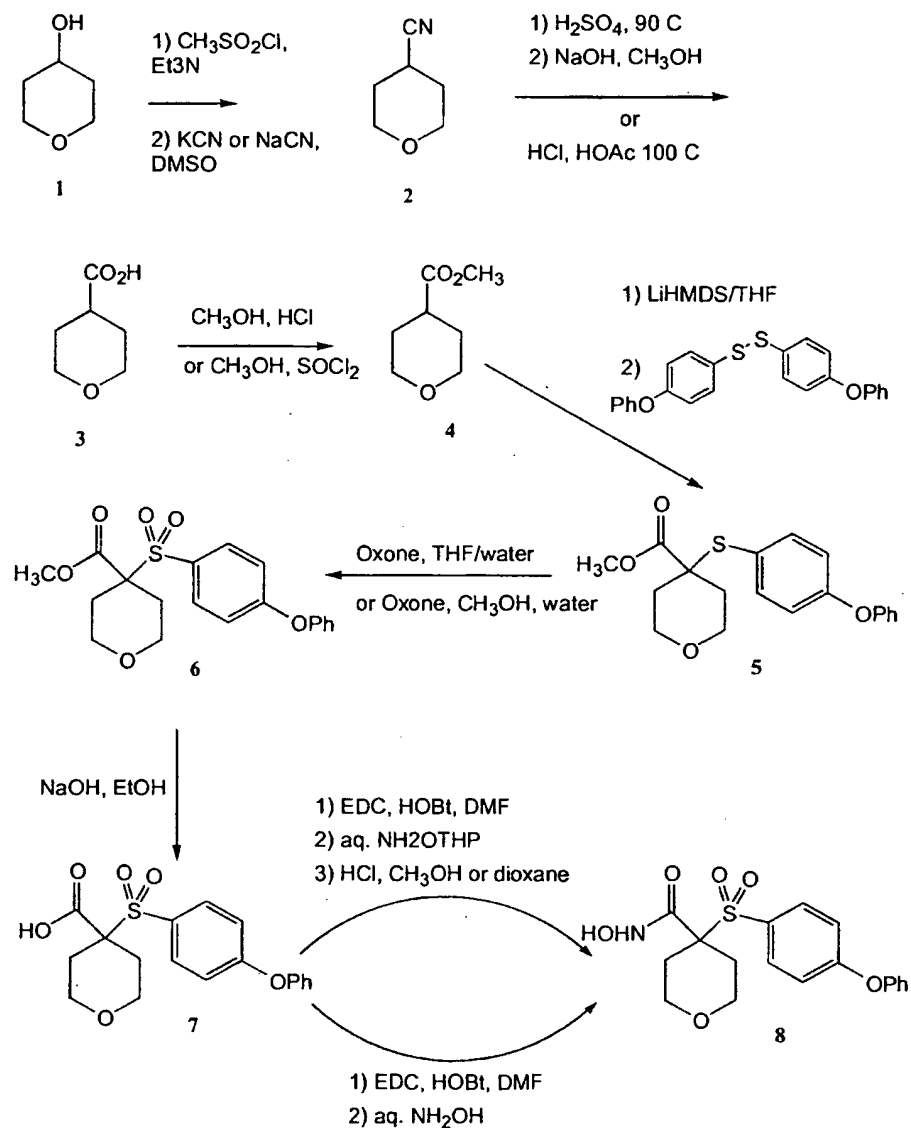
In a similar manner, the following analogs can be made.



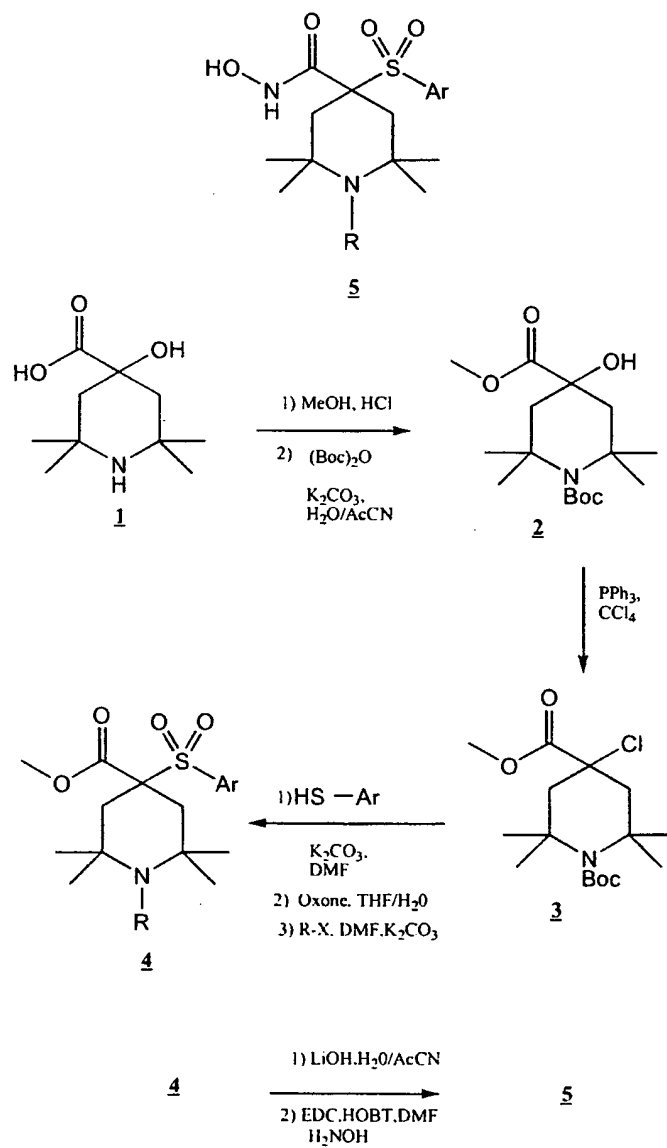
Scheme 14



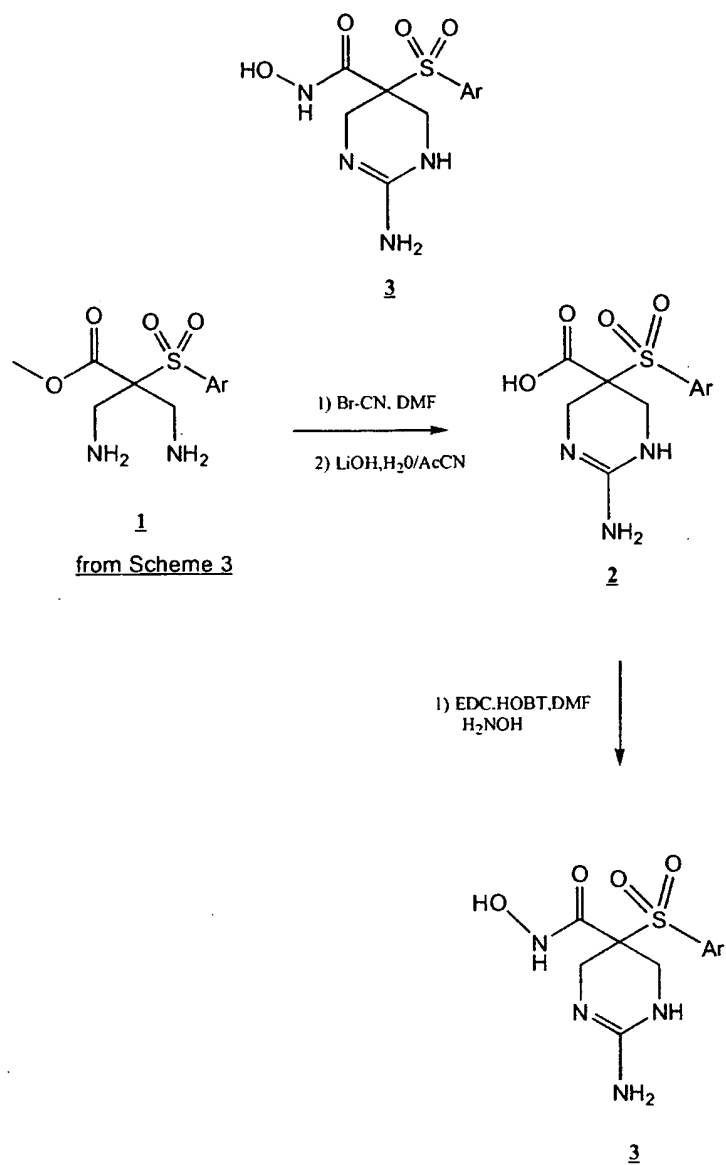
Scheme 15



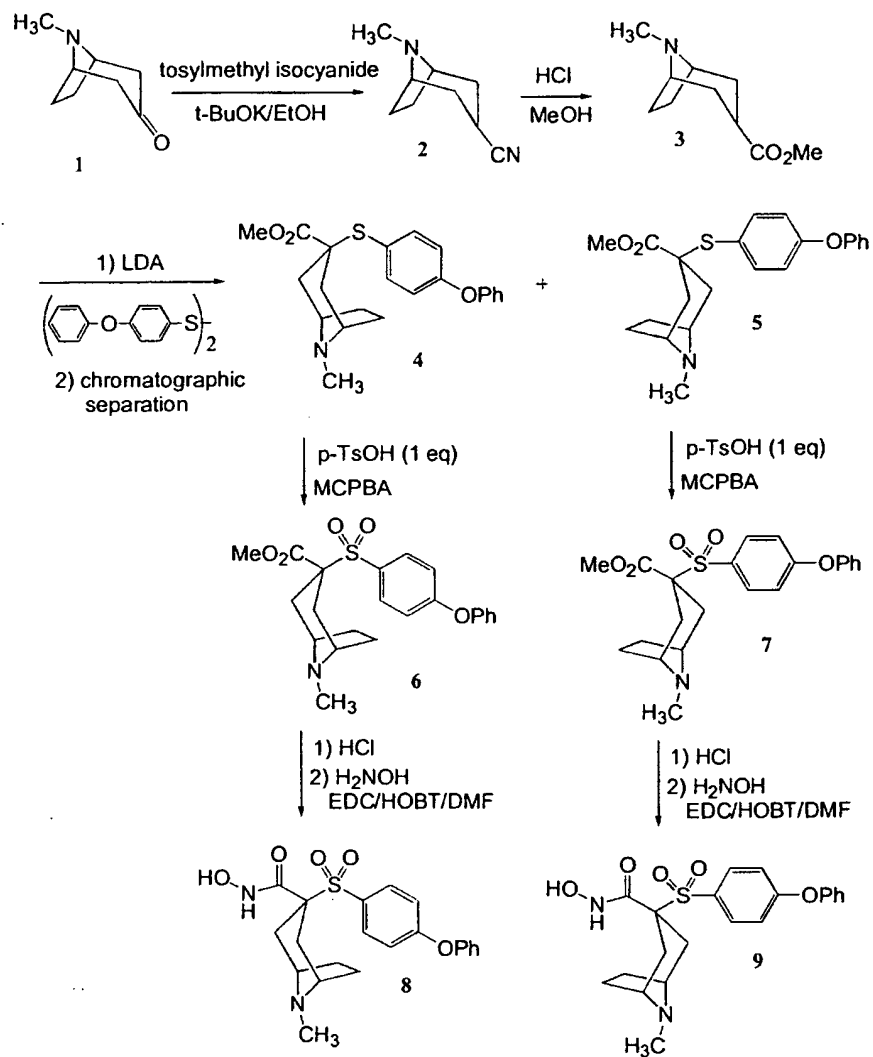
Scheme 16



Scheme 17



Scheme 18



Scheme 19

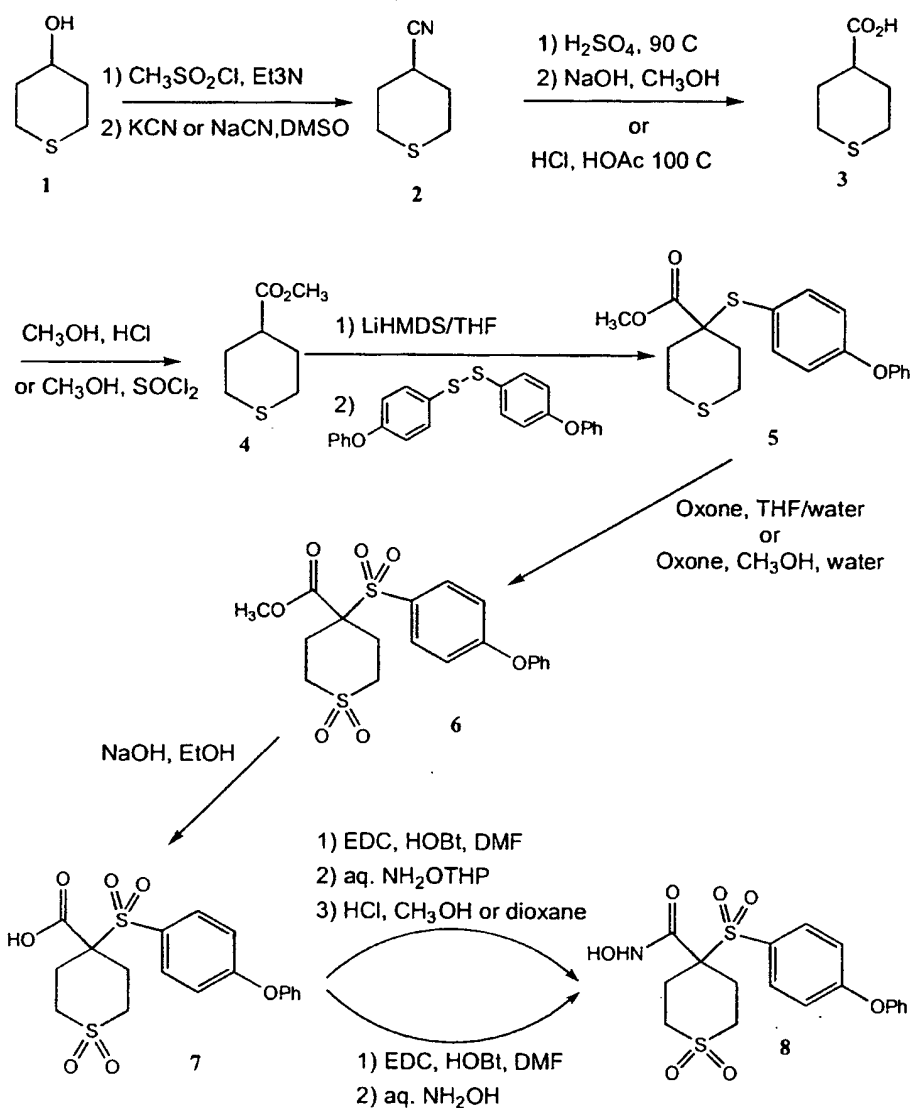


Table 1 through Table 150, below, show several contemplated aromatic sulfone hydroxamic acid inhibitor compounds or structural formulas that illustrate substituent groups. Each group of

compounds is illustrated by a generic formula, or formulae, followed by a series of preferred moieties or groups that constitute various substituents that can be attached at the position clearly shown in the generic structure. The substituent symbols, e.g., R1 and R2 and R3, are as shown in each Table, and are typically not those used before. One or two bonds (wavy lines) are shown with those substituents to indicate the respective positions of attachment in the illustrated compound. This system is well known in the chemical communication arts and is widely used in scientific papers and presentations. For example in Table 2, R1 and R2 together with the atoms to which they are bonded is the variable group with the structural entities that can substitute for R1 and R2 together shown in the balance of that table.

Table 1

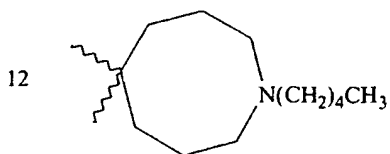
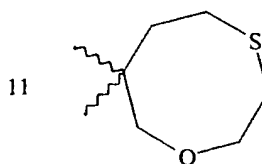
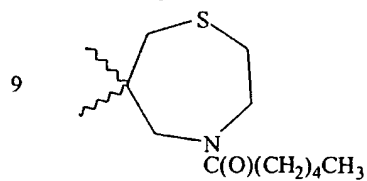
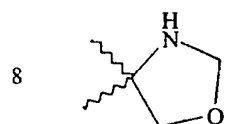
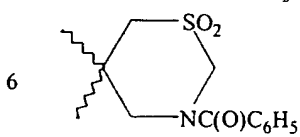
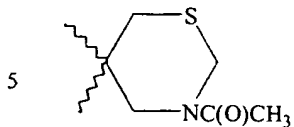
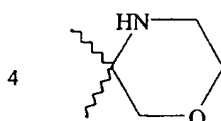
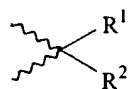
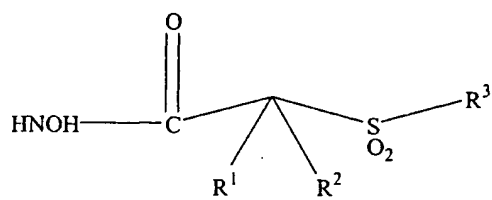


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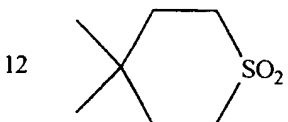
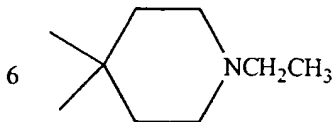
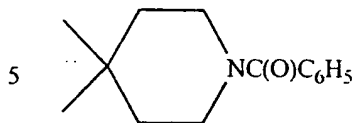
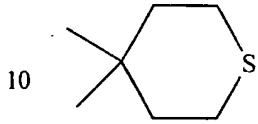
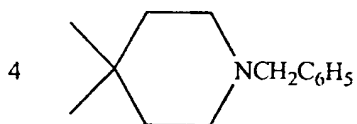
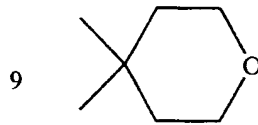
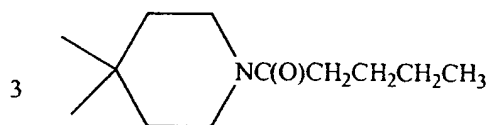
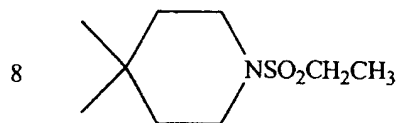
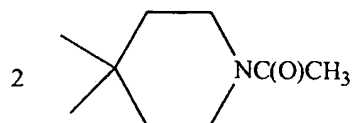
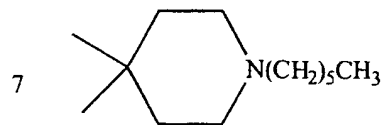
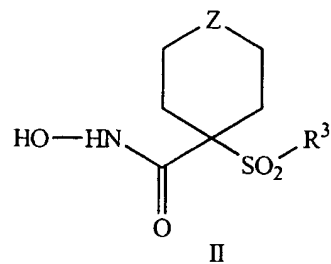


Table 3

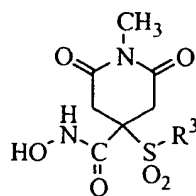
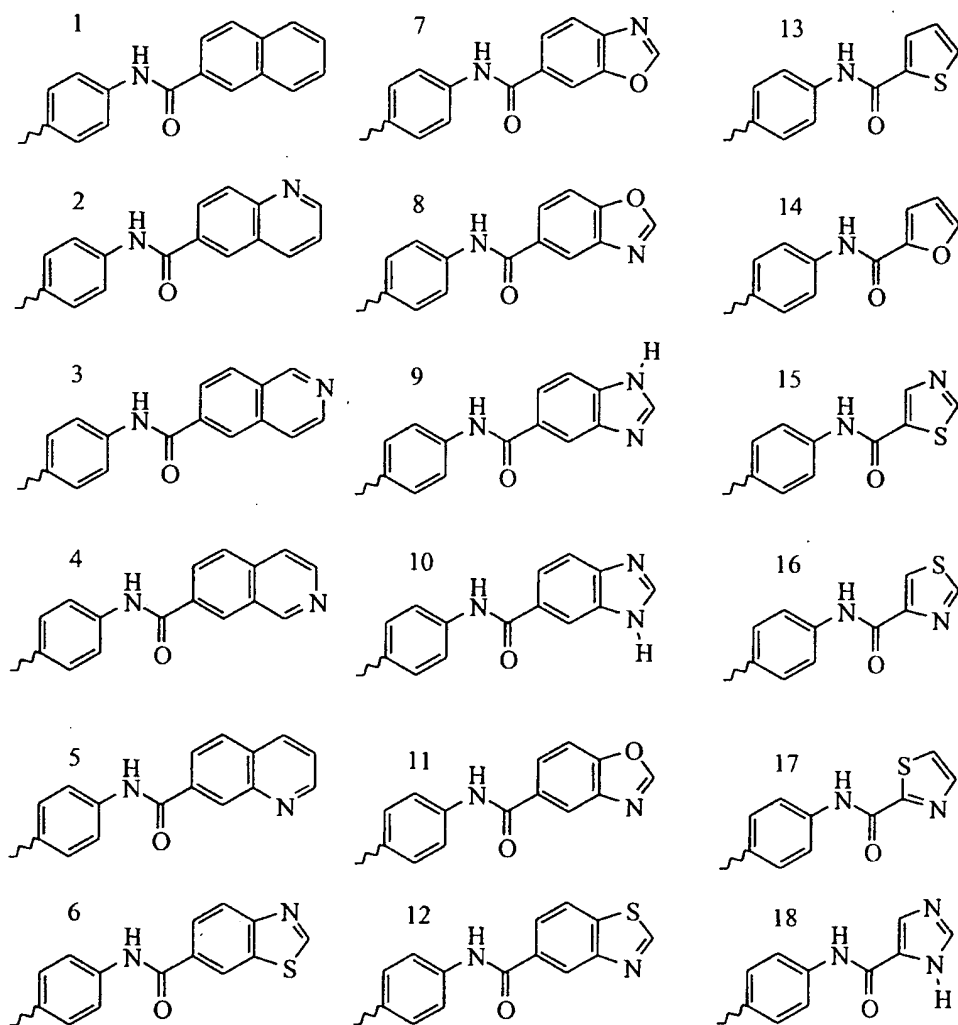
 R^3 

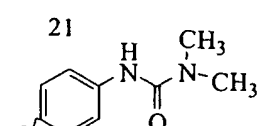
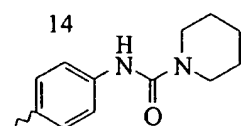
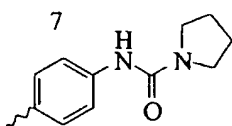
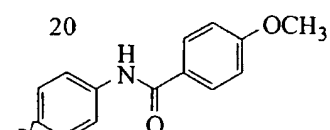
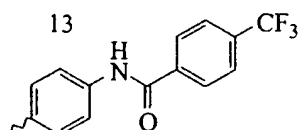
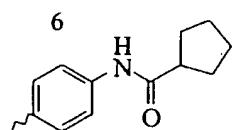
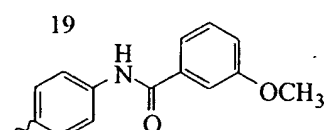
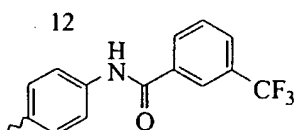
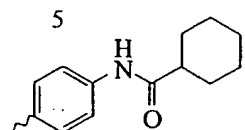
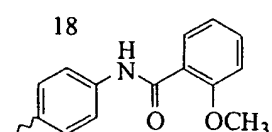
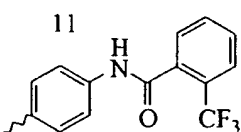
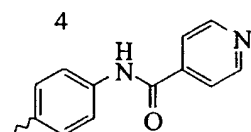
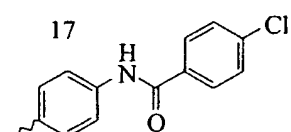
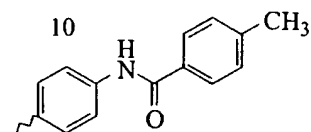
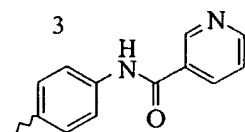
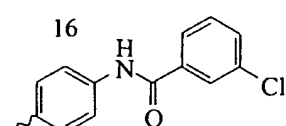
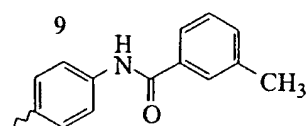
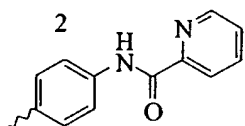
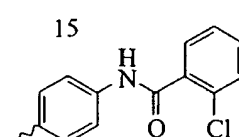
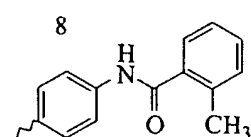
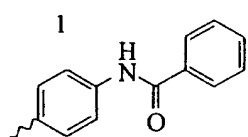
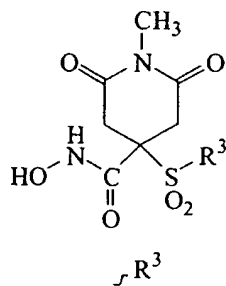
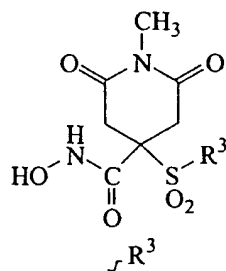
Table 4

Table 5



1 	9 	16
2 	10 	17
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4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

Table 6

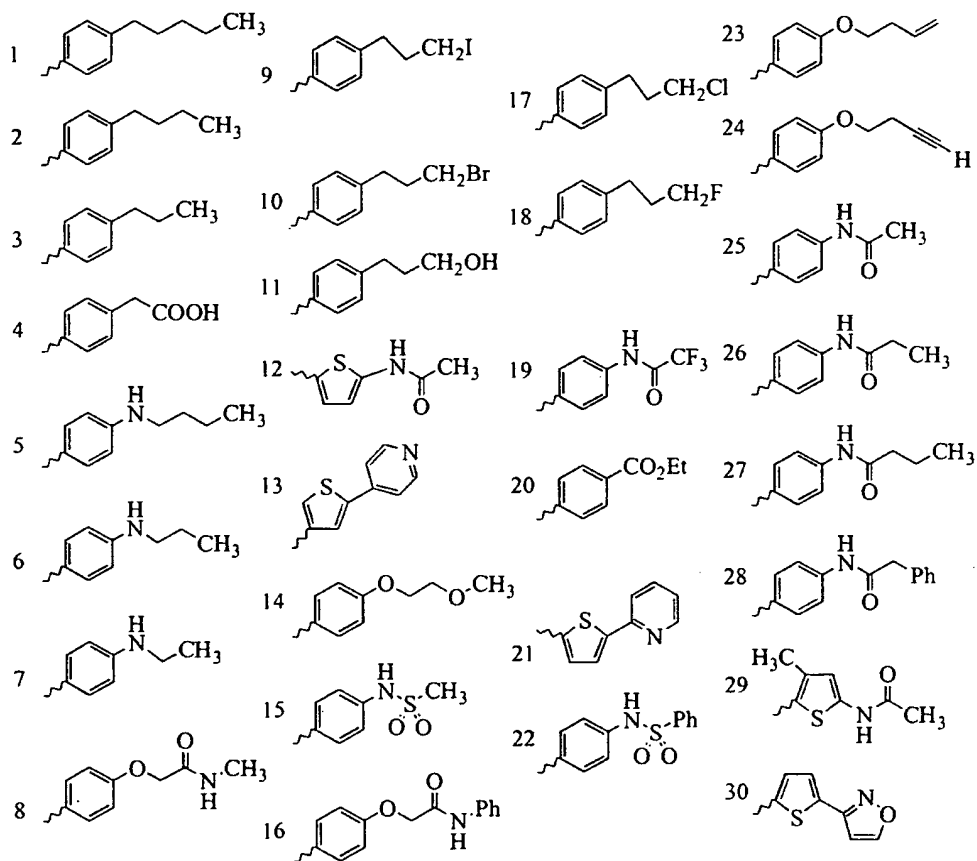
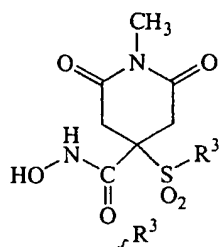


Table 7

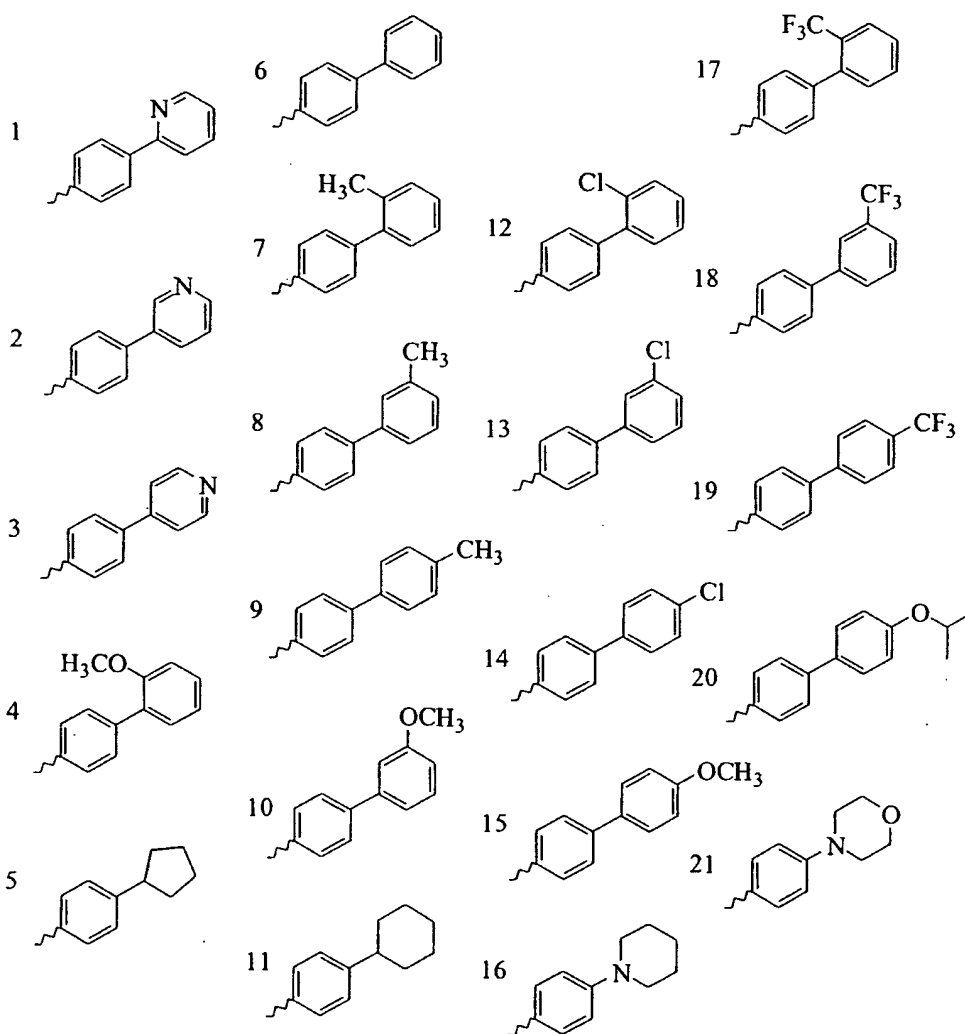
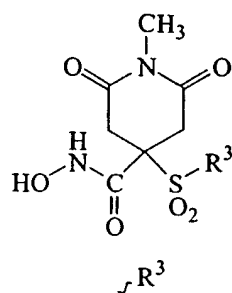


Table 8

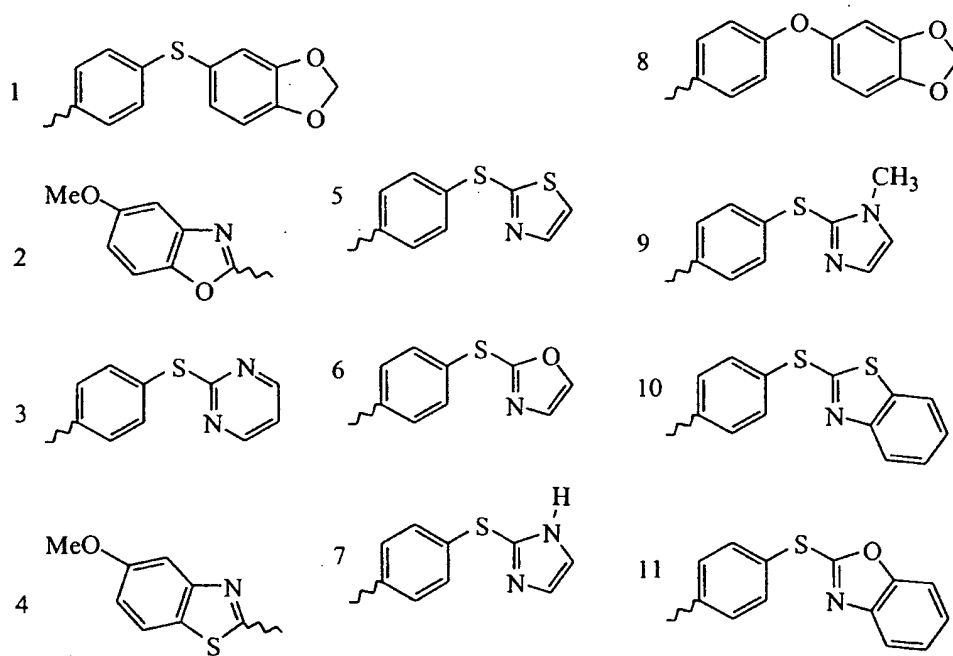
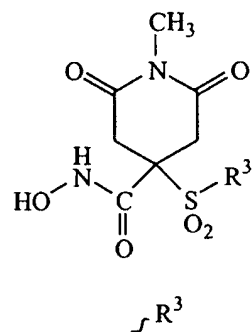
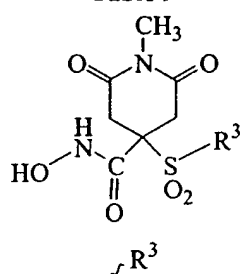


Table 9



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4	11	18
5	12	19
6	13	20
7	14	21

Table 10

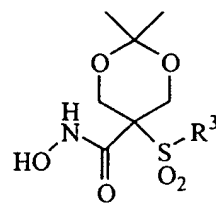
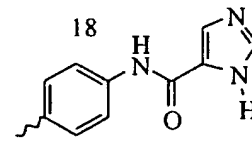
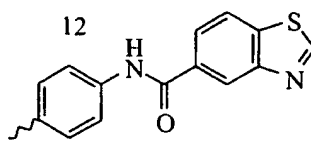
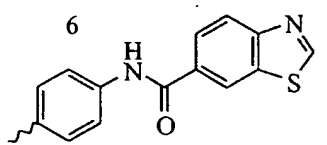
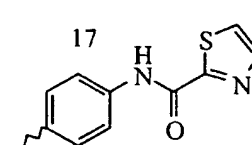
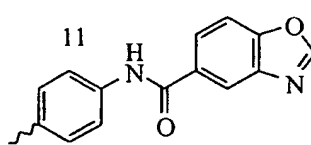
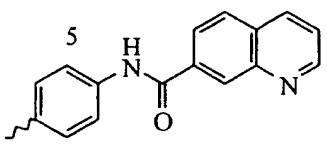
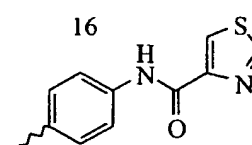
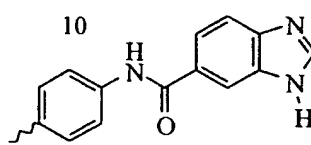
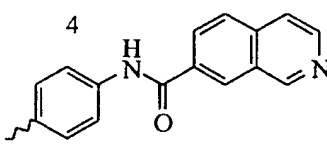
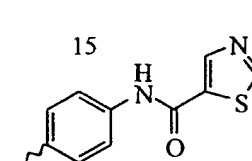
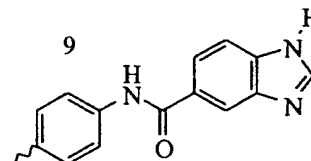
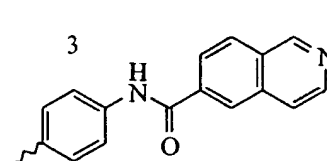
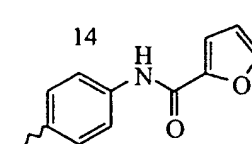
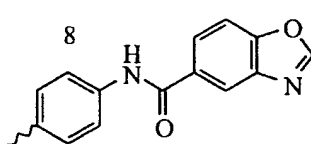
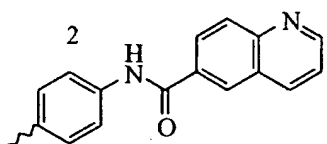
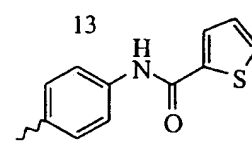
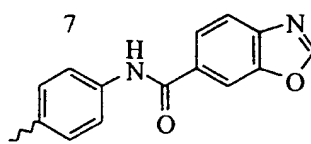
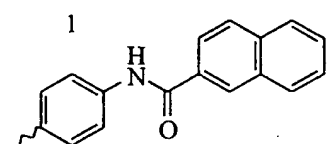
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Table 11

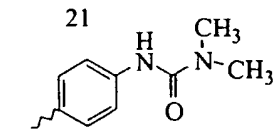
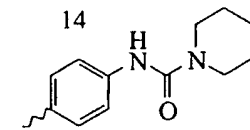
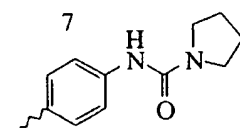
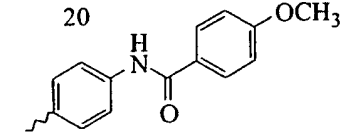
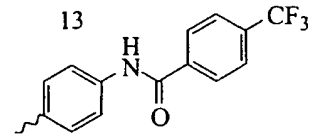
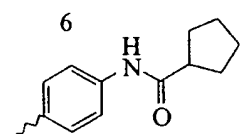
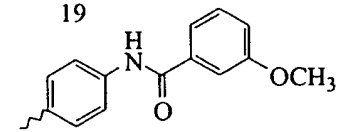
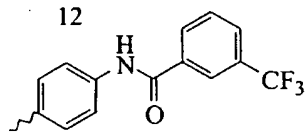
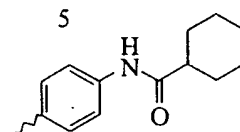
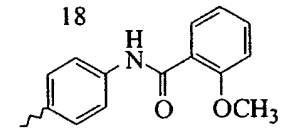
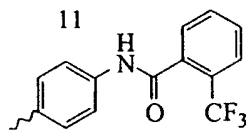
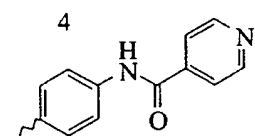
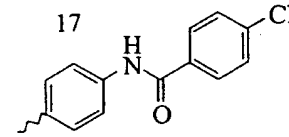
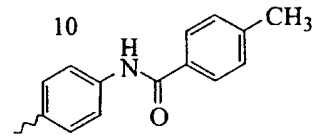
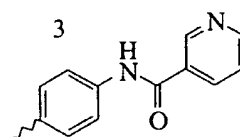
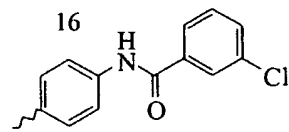
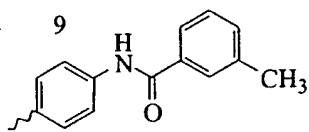
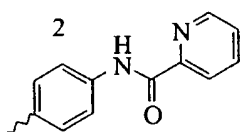
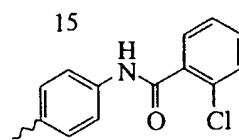
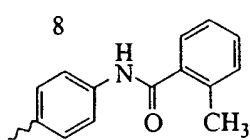
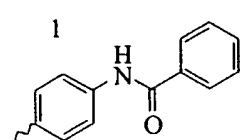
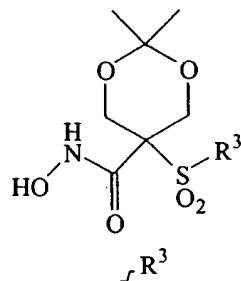
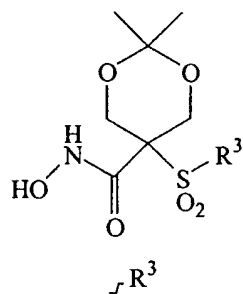


Table 12



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

Table 13

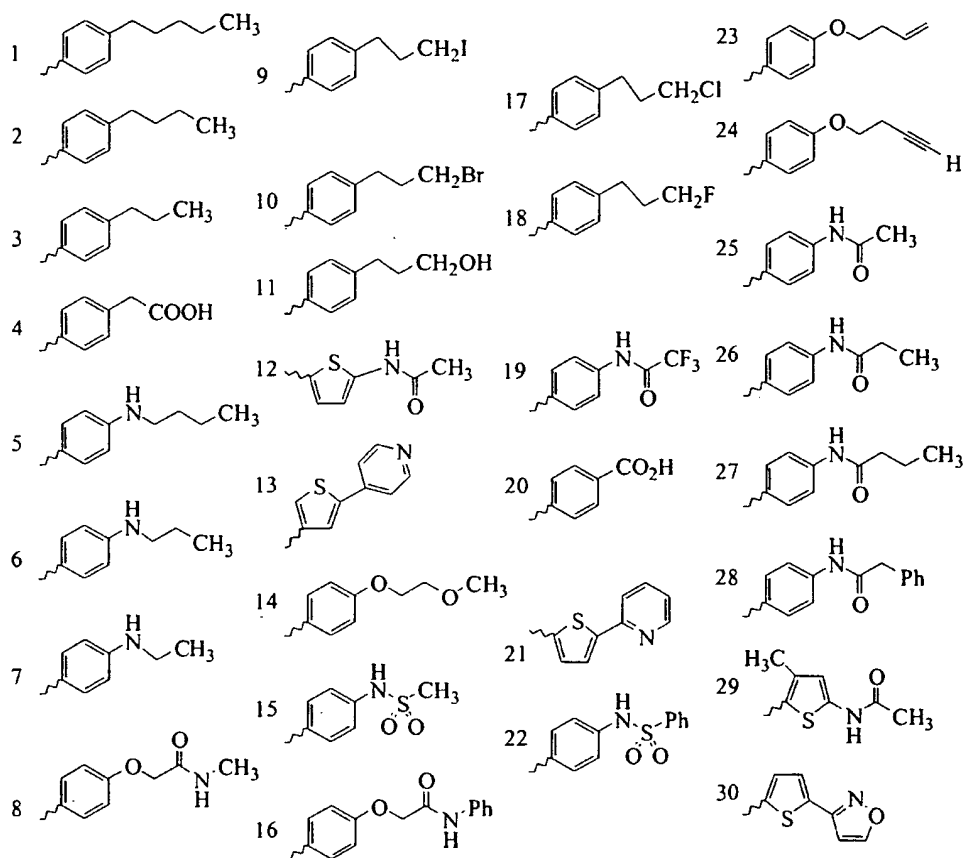
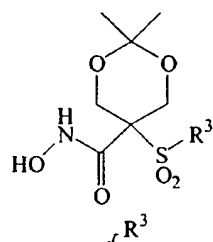


Table 14

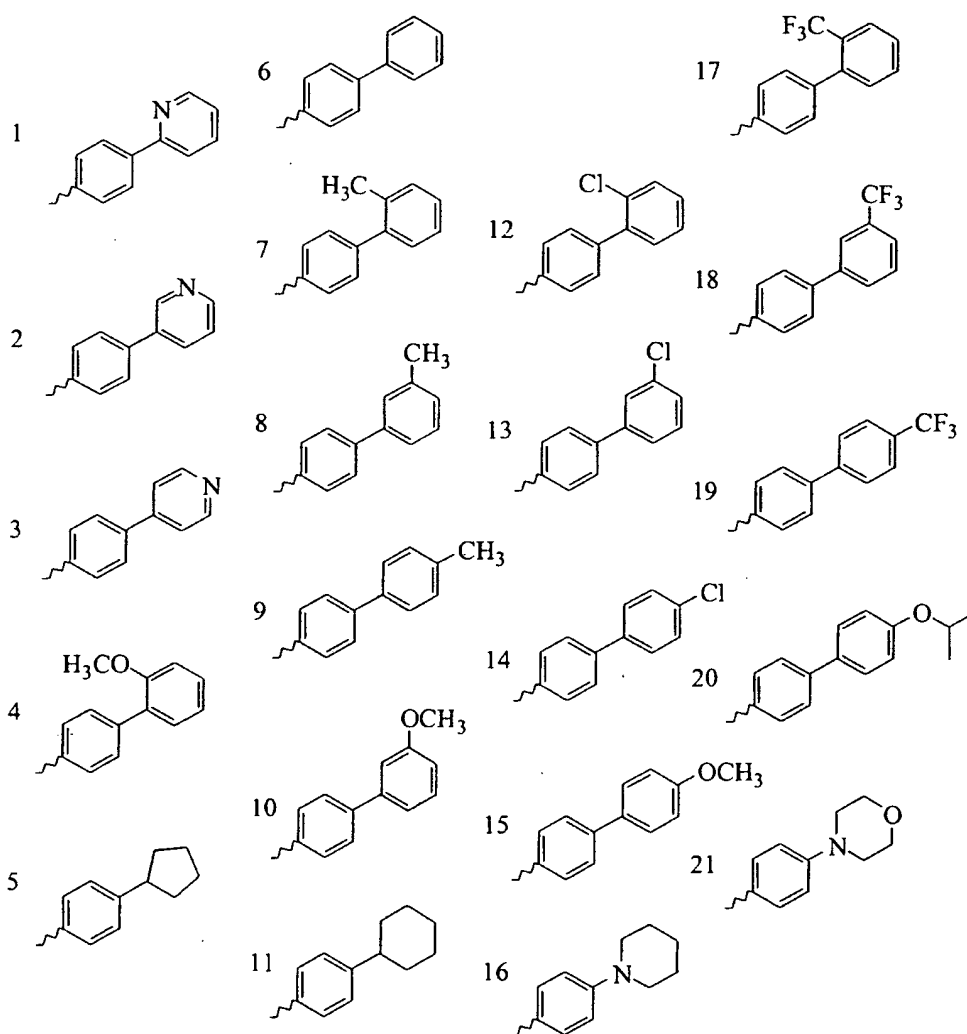
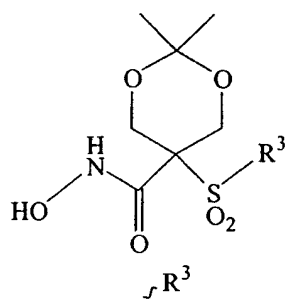


Table 15

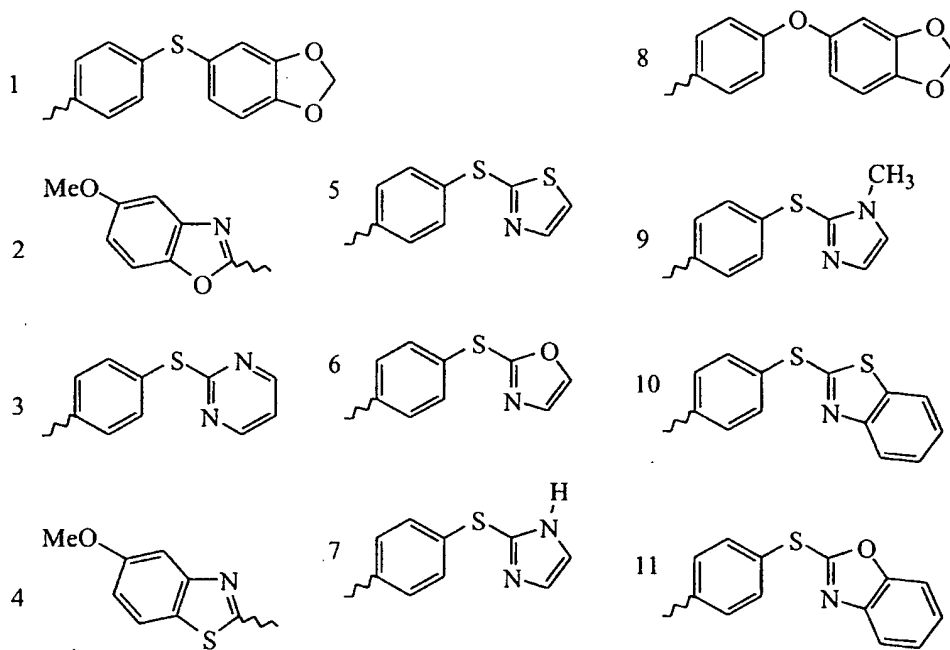
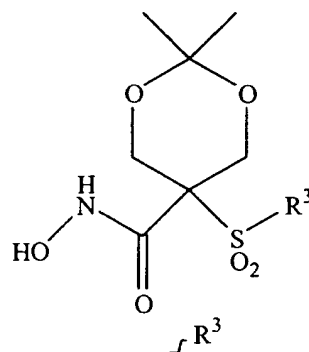
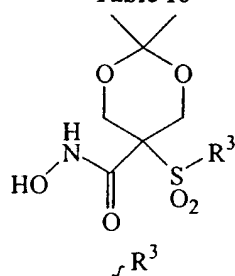


Table 16



1	8	15
2	9	16
3	10	17
4	11	18
5	12	19
6	13	20
7	14	21

Table 17

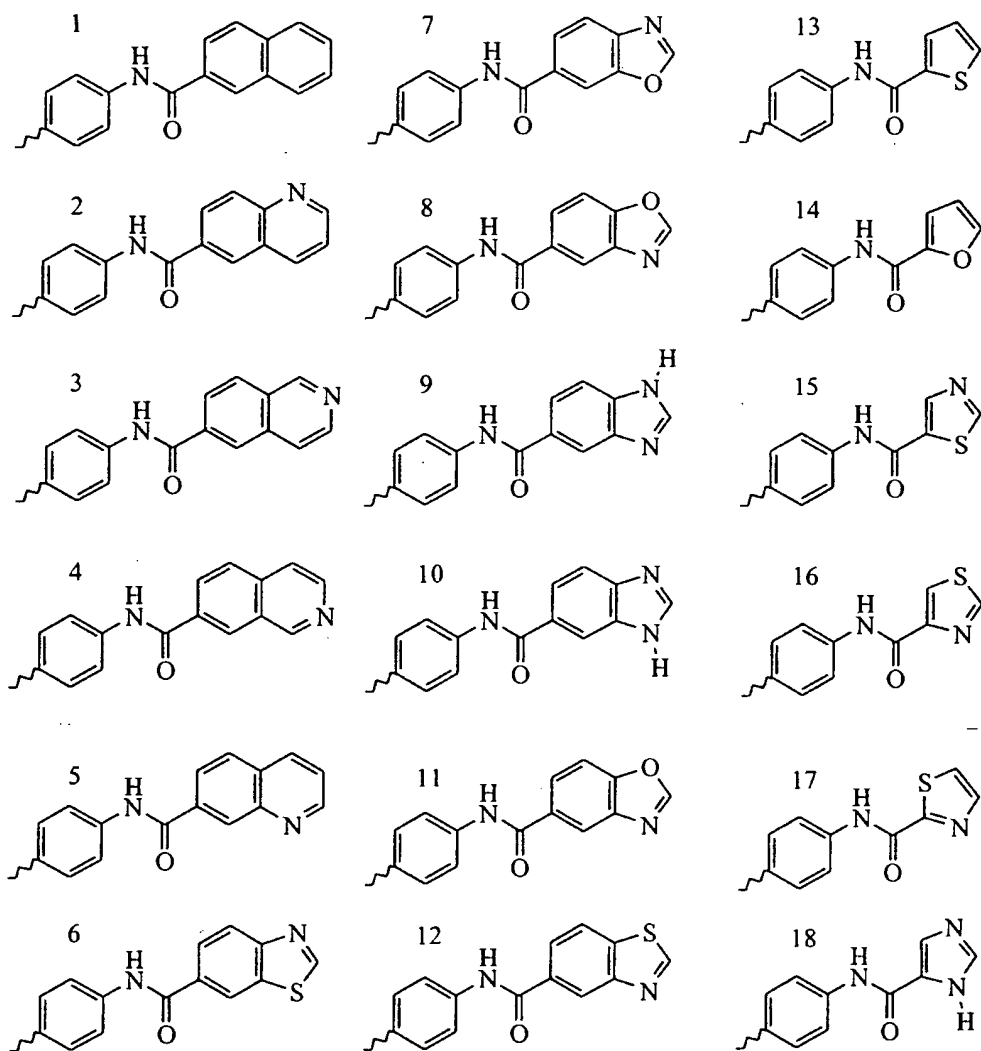
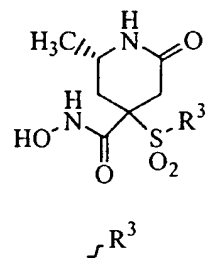


Table 18

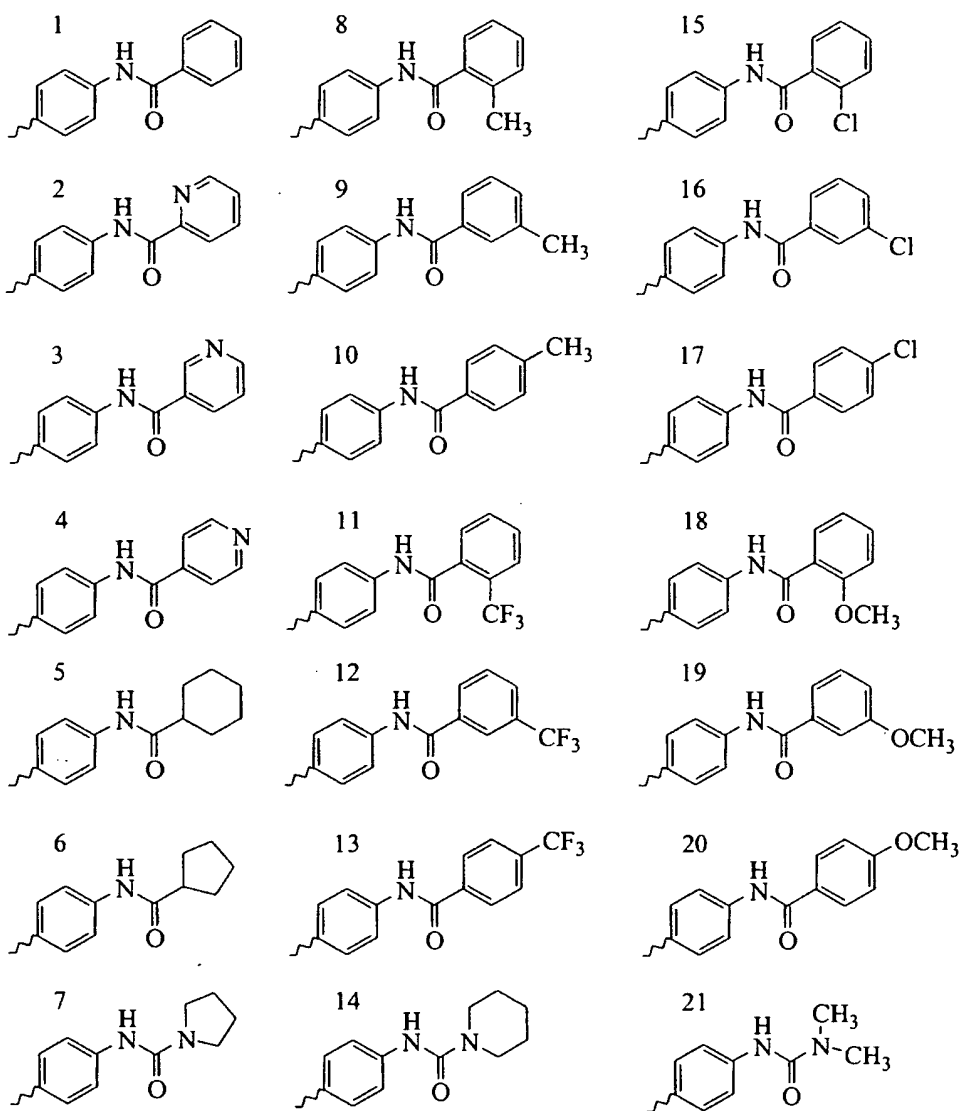
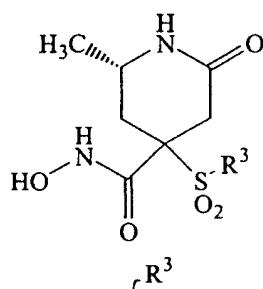
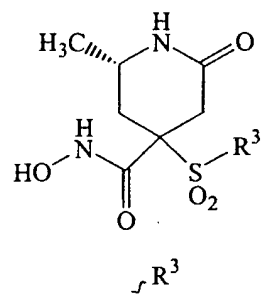


Table 19



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

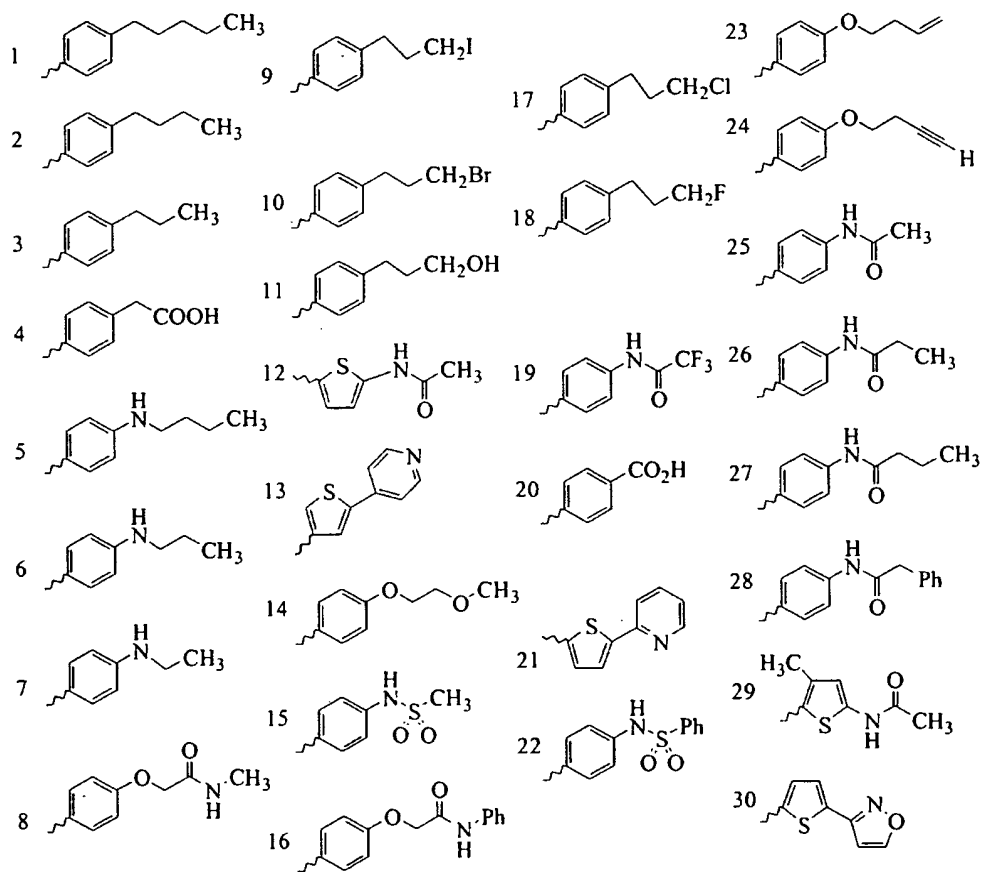
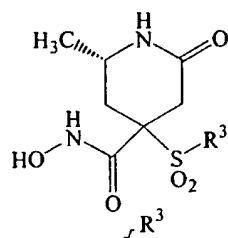
Table 20

Table 21

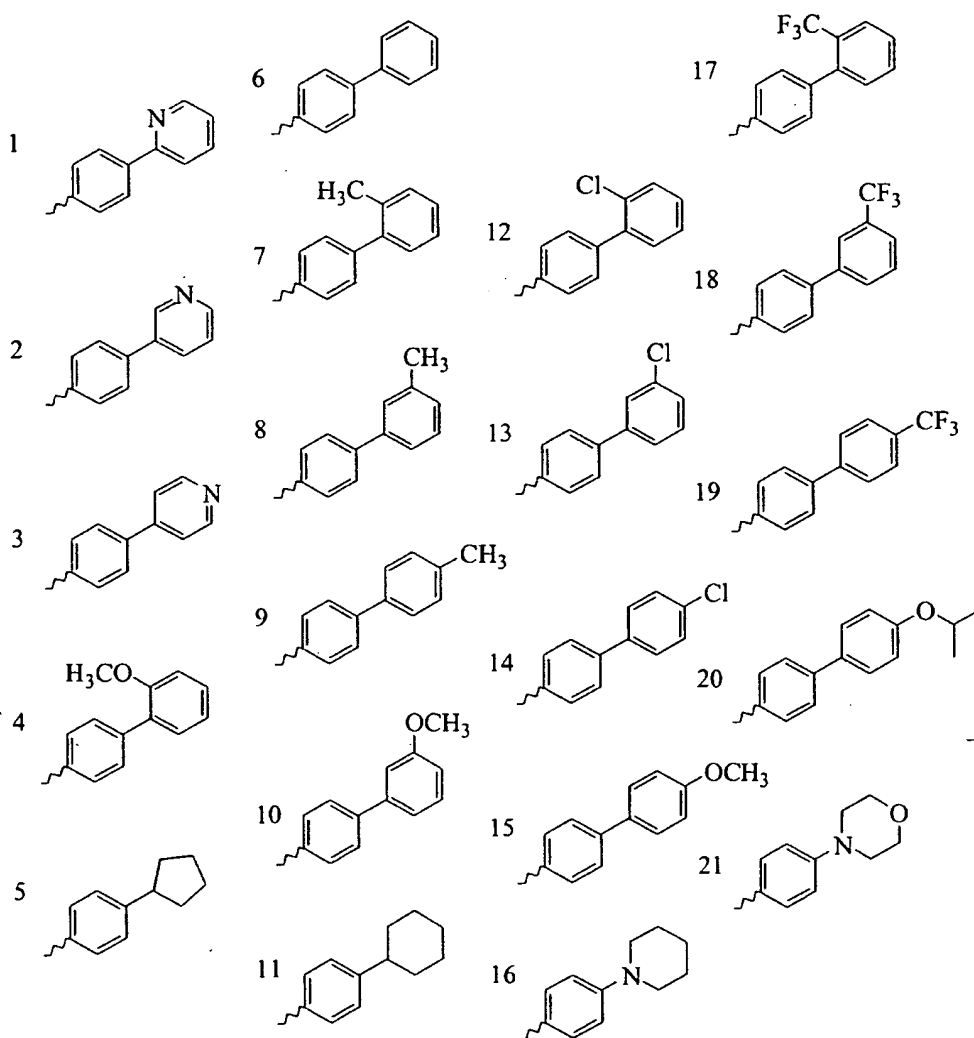
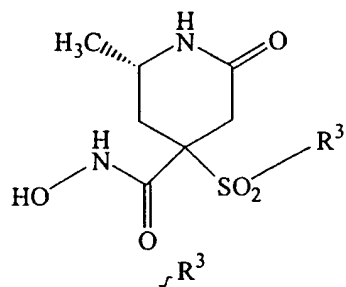


Table 22

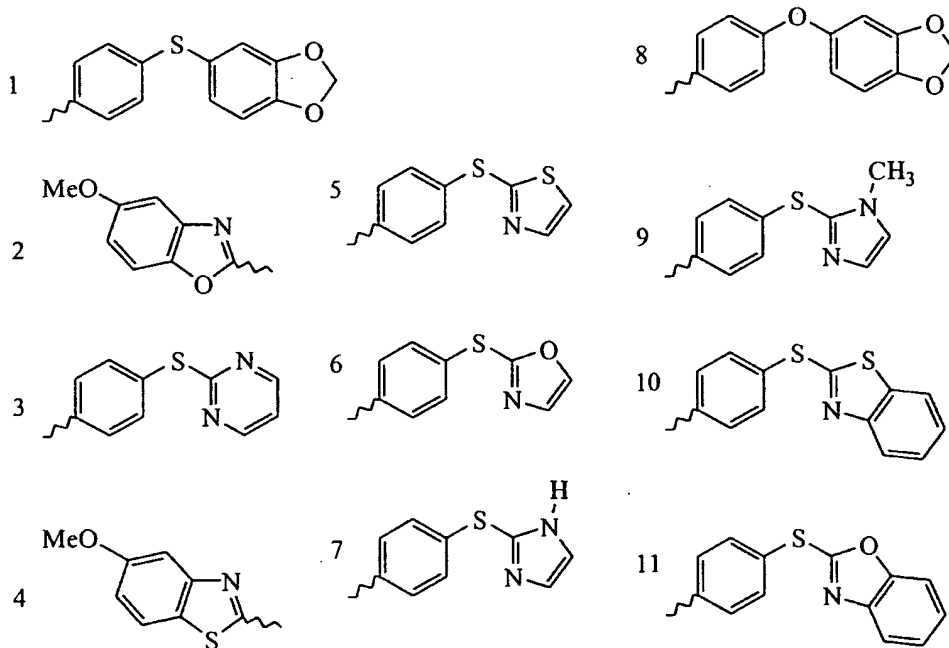
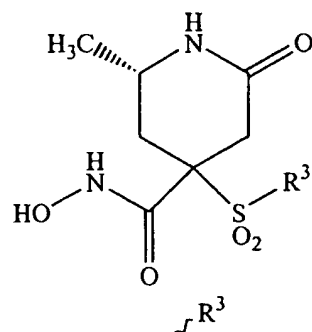


Table 23

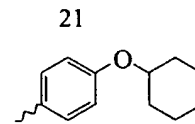
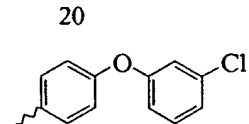
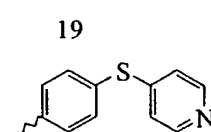
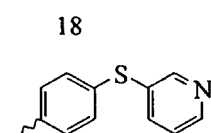
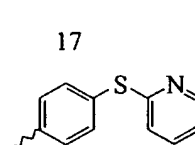
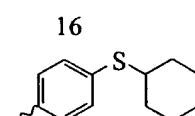
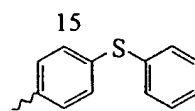
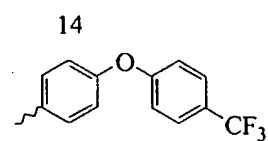
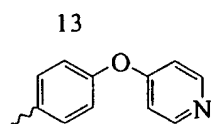
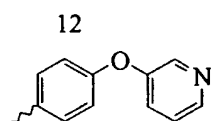
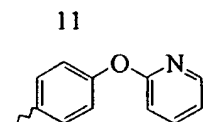
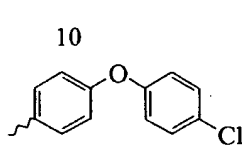
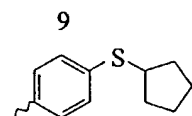
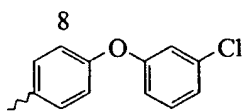
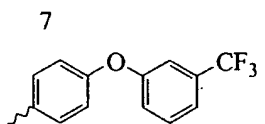
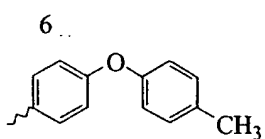
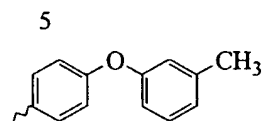
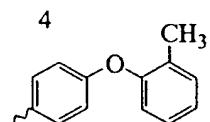
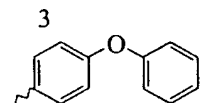
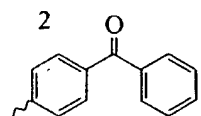
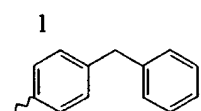
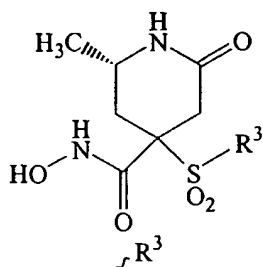


Table 24

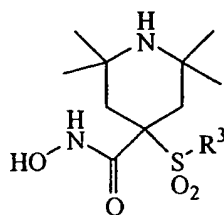
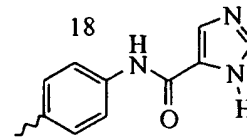
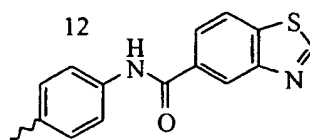
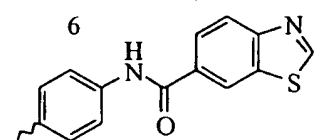
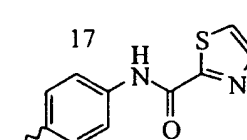
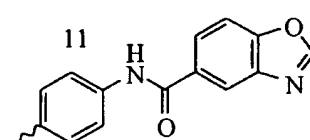
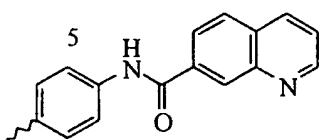
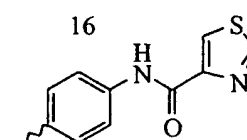
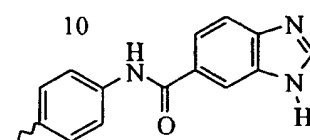
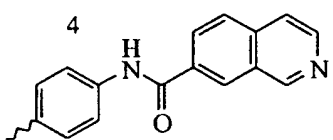
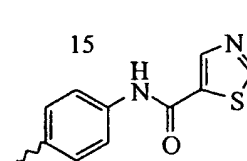
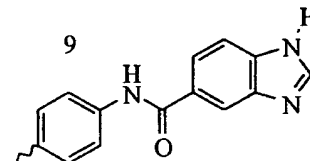
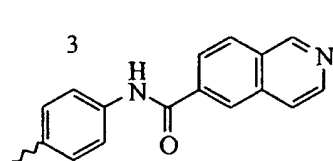
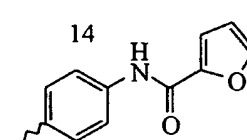
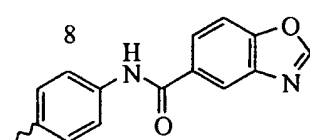
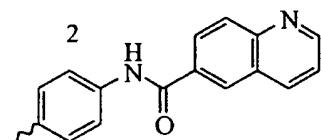
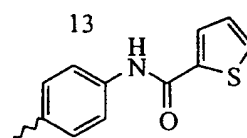
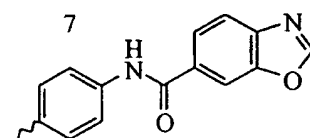
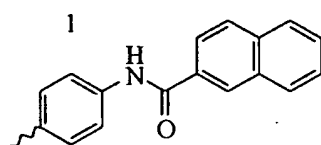
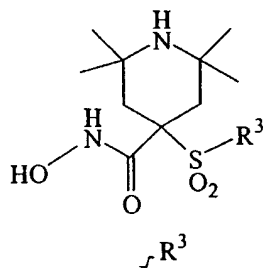
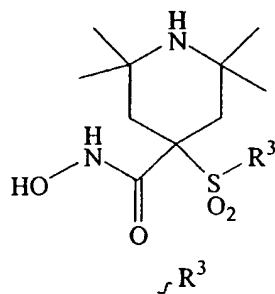
 R^3 

Table 25



1 	8 	15
2 	9 	16
3 	10 	17
4 	11 	18
5 	12 	19
6 	13 	20
7 	14 	21

Table 26



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

Table 27

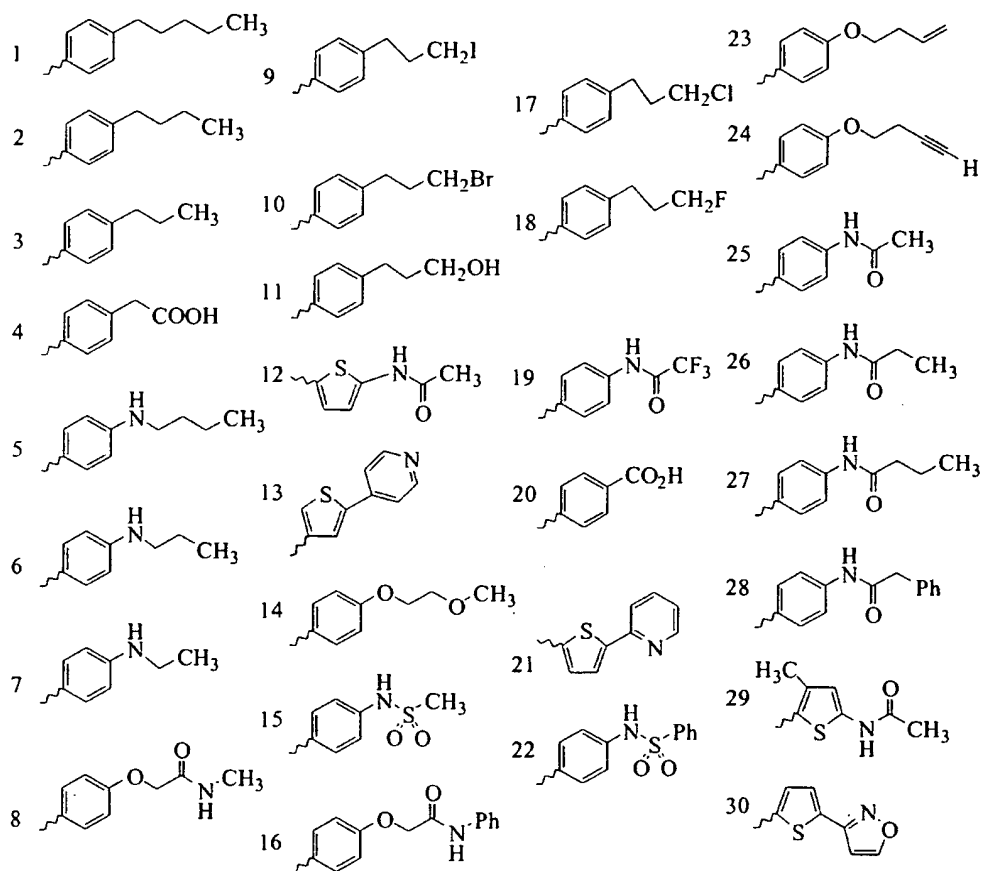
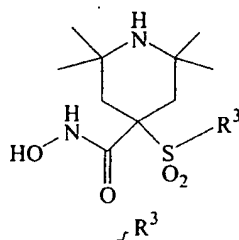


Table 28

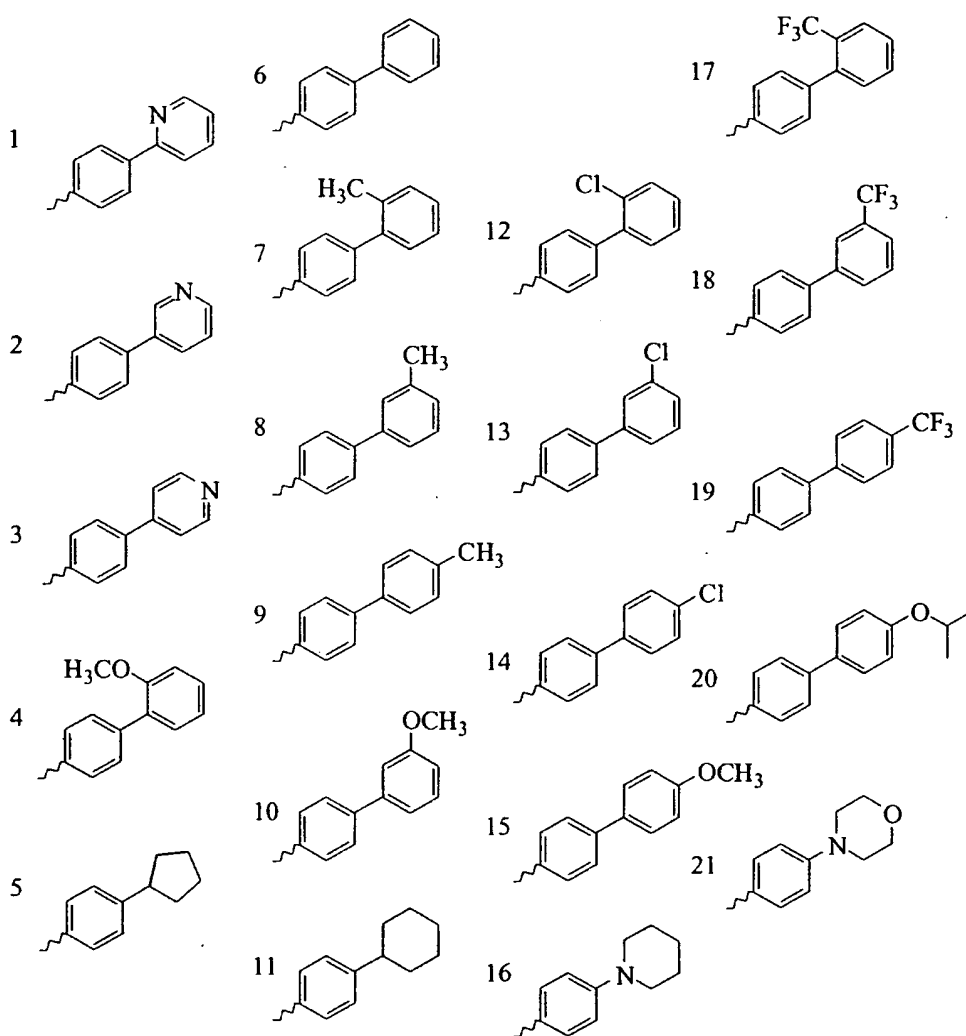
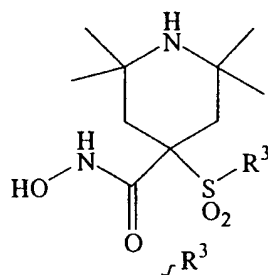


Table 29

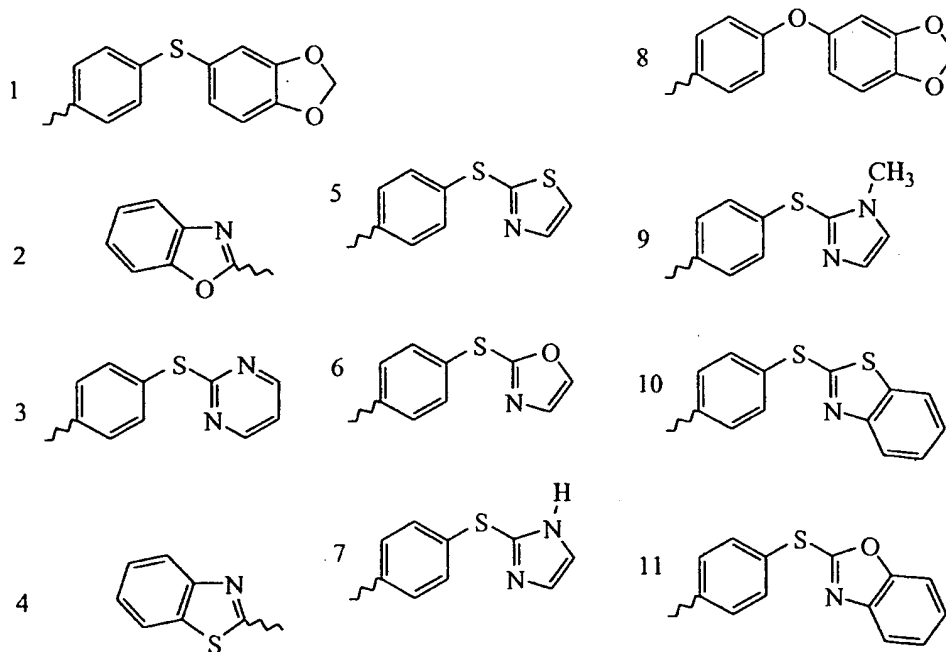
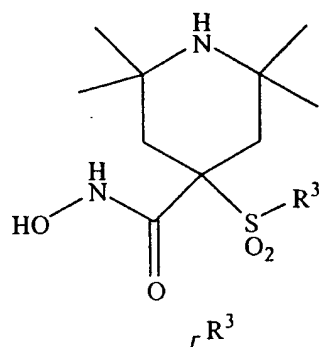
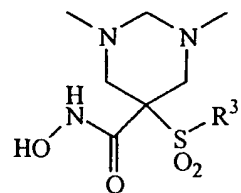


Table 30



R^3

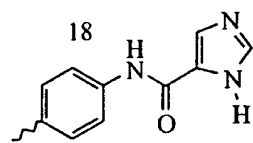
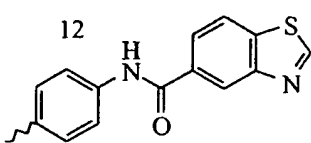
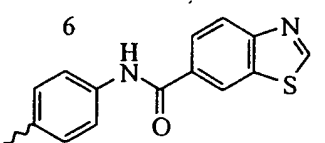
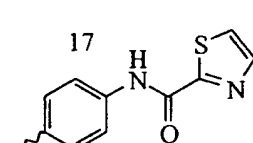
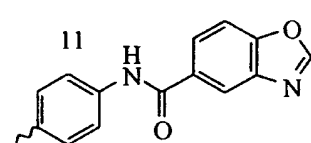
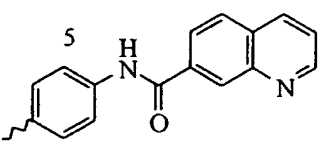
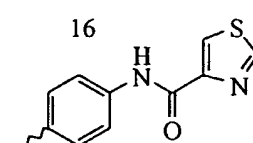
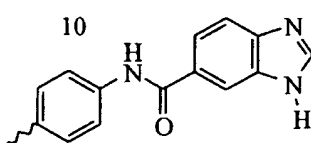
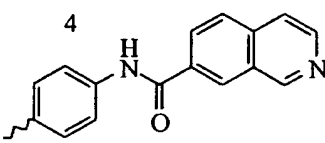
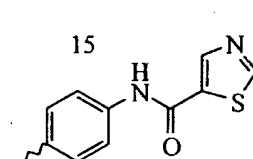
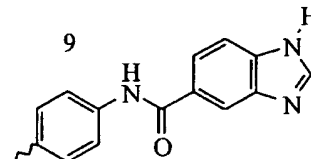
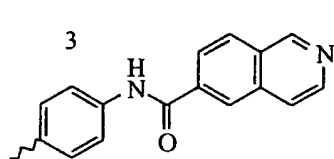
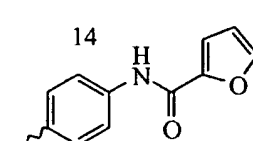
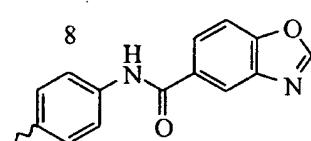
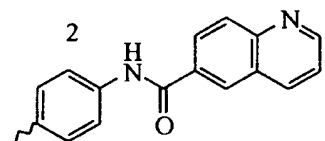
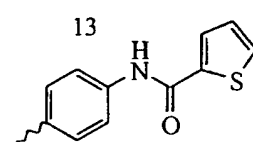
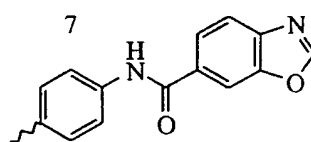
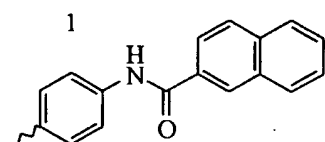


Table 31

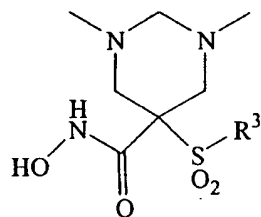
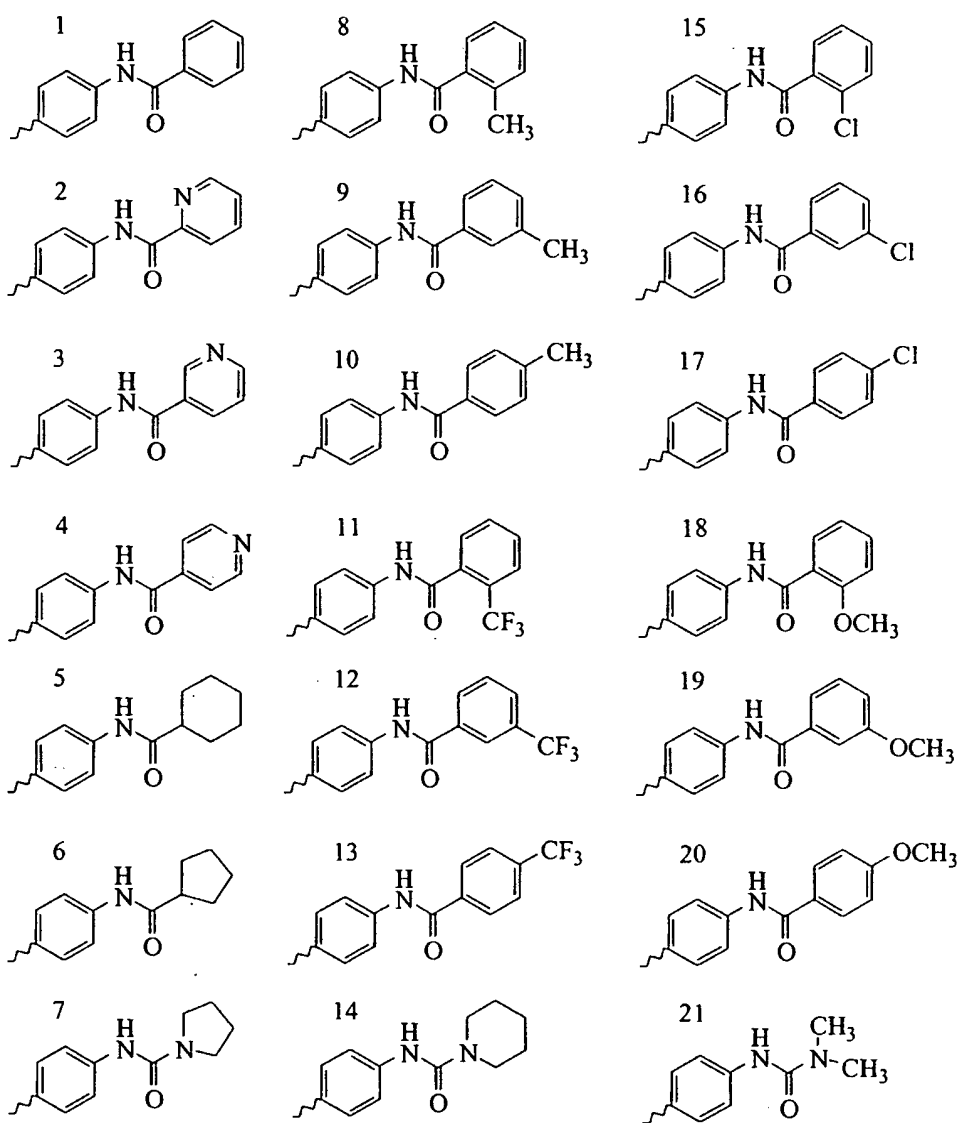
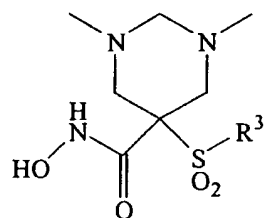
 R^3 

Table 32

 R^3

1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

Table 33

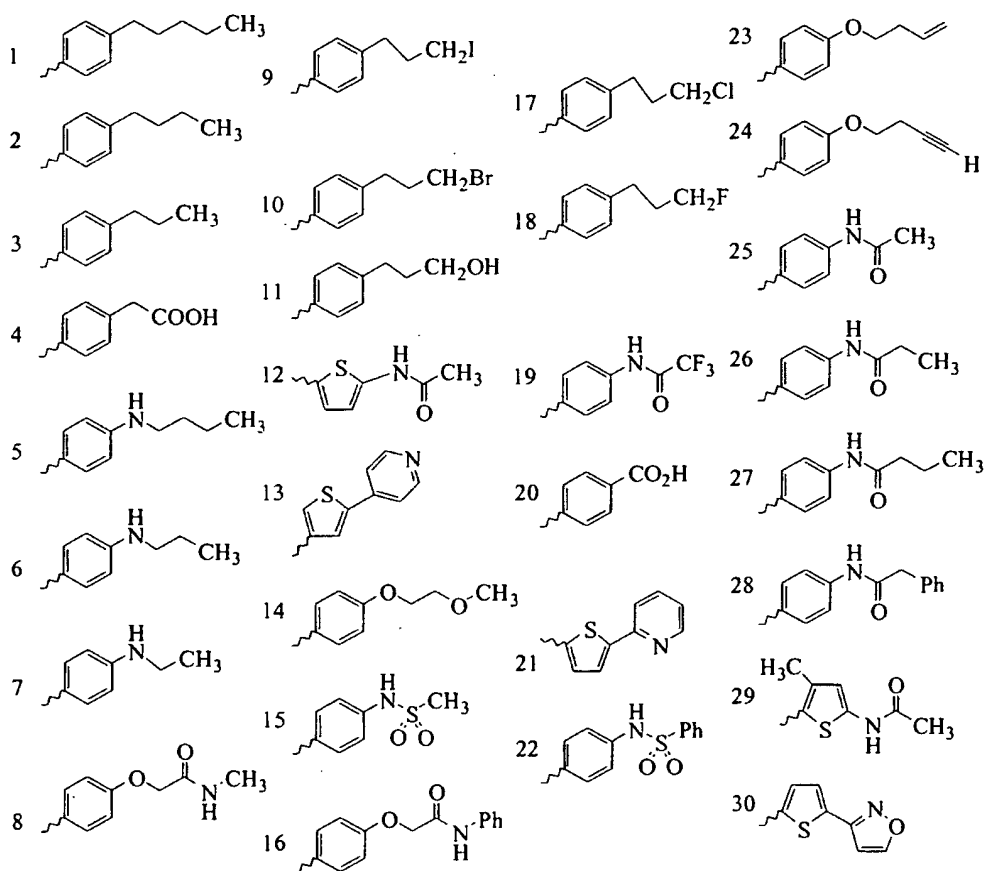
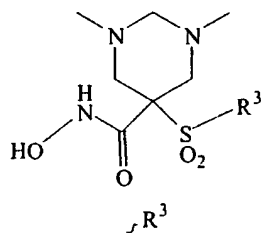


Table 34

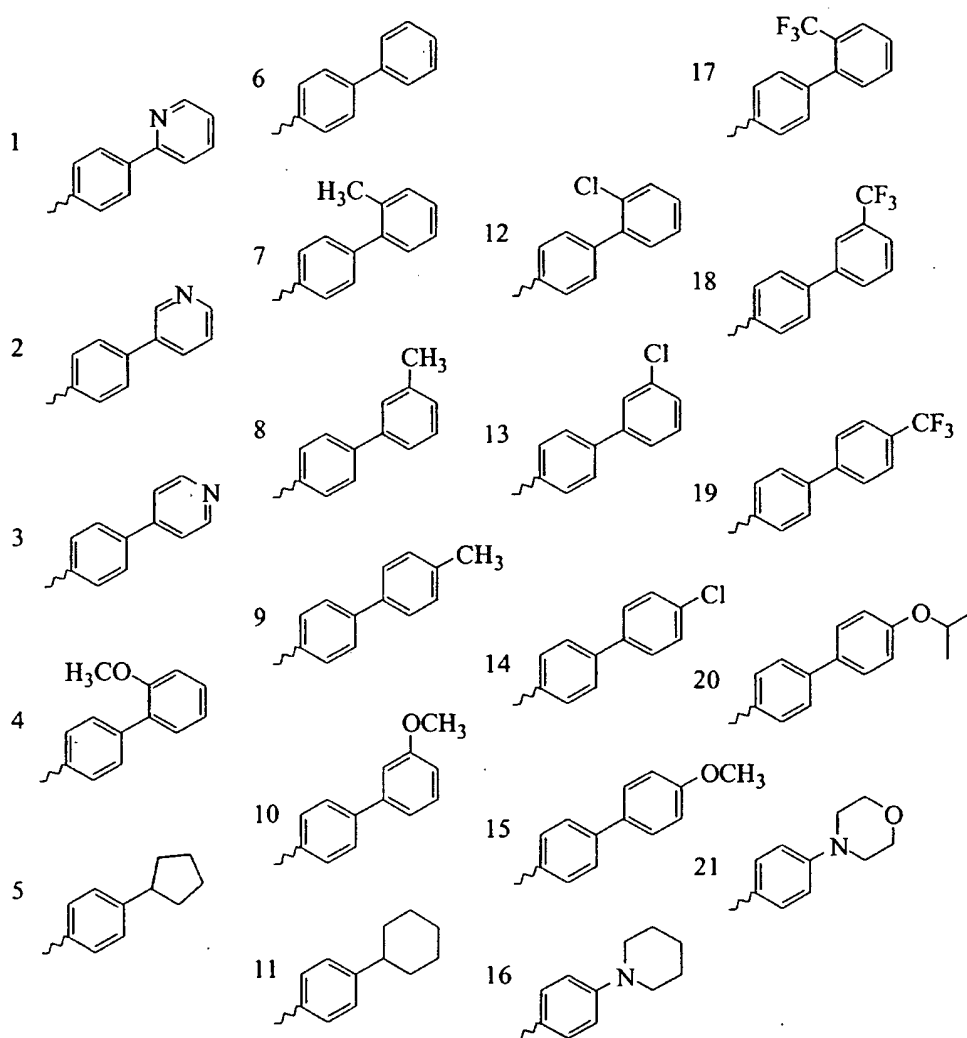
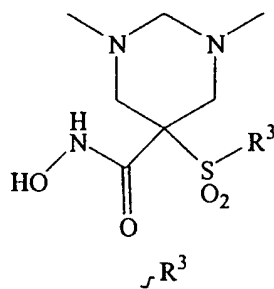


Table 35

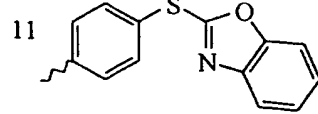
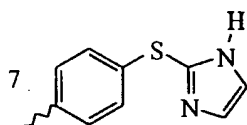
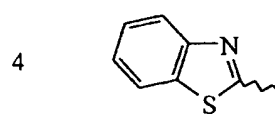
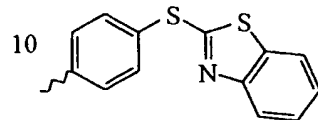
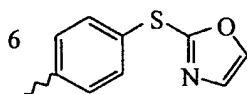
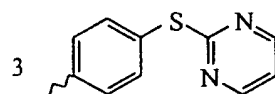
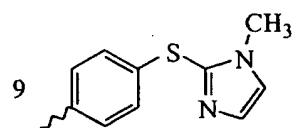
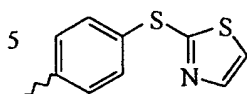
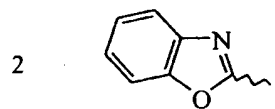
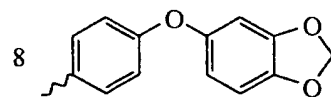
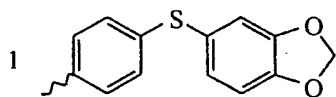
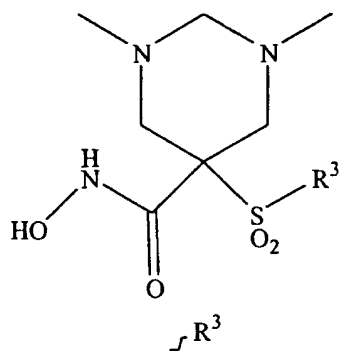
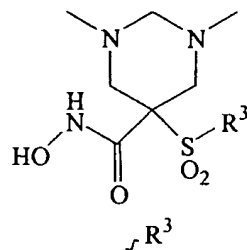


Table 36



1	8	15
2	9	16
3	10	17
4	11	18
5	12	19
6	13	20
7	14	21

Table 37

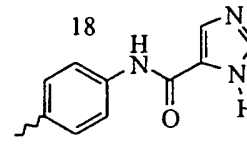
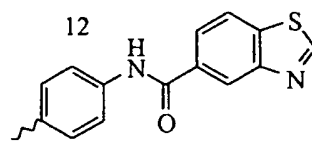
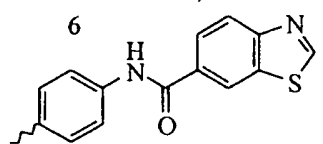
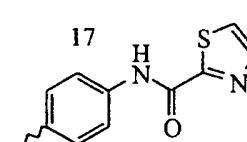
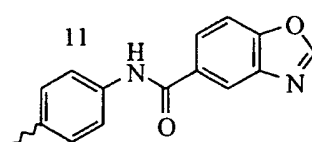
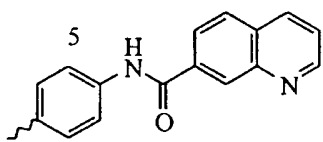
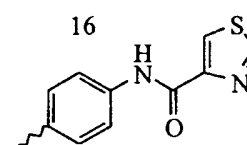
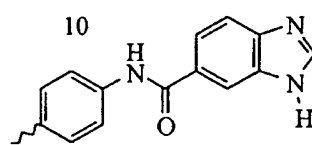
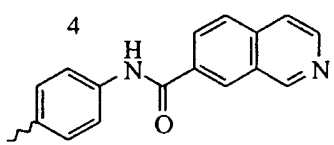
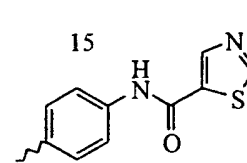
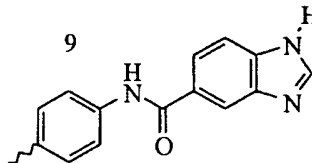
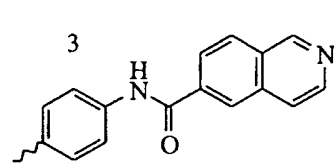
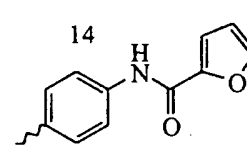
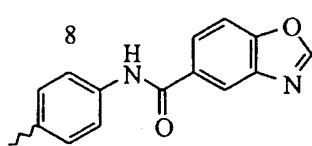
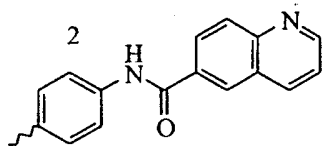
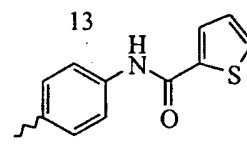
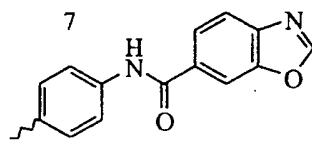
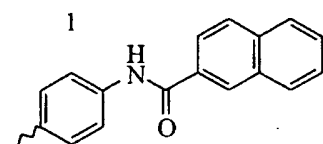
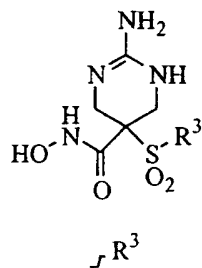


Table 38

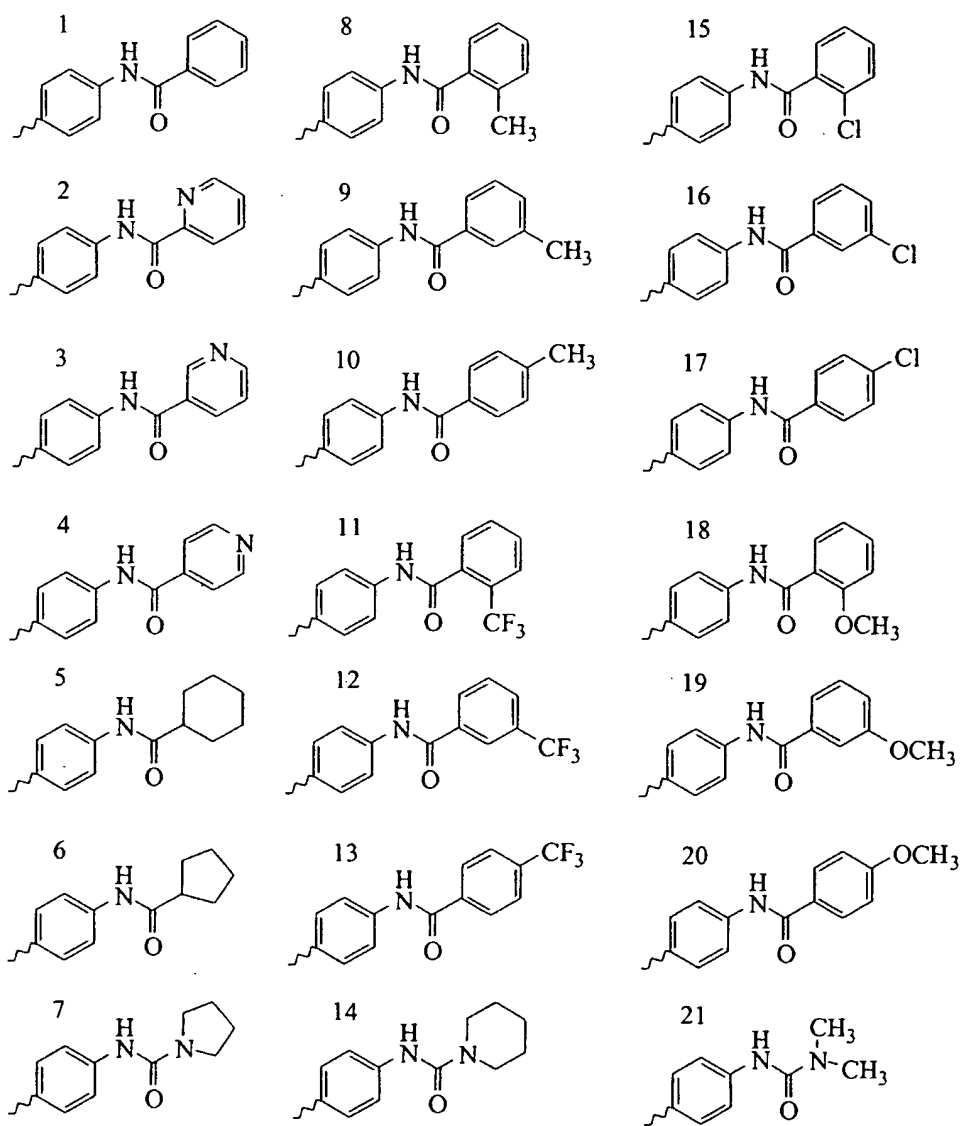
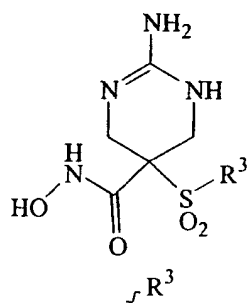
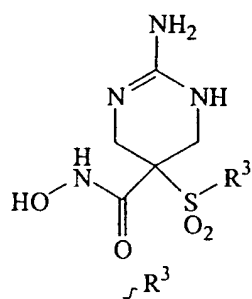


Table 39



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

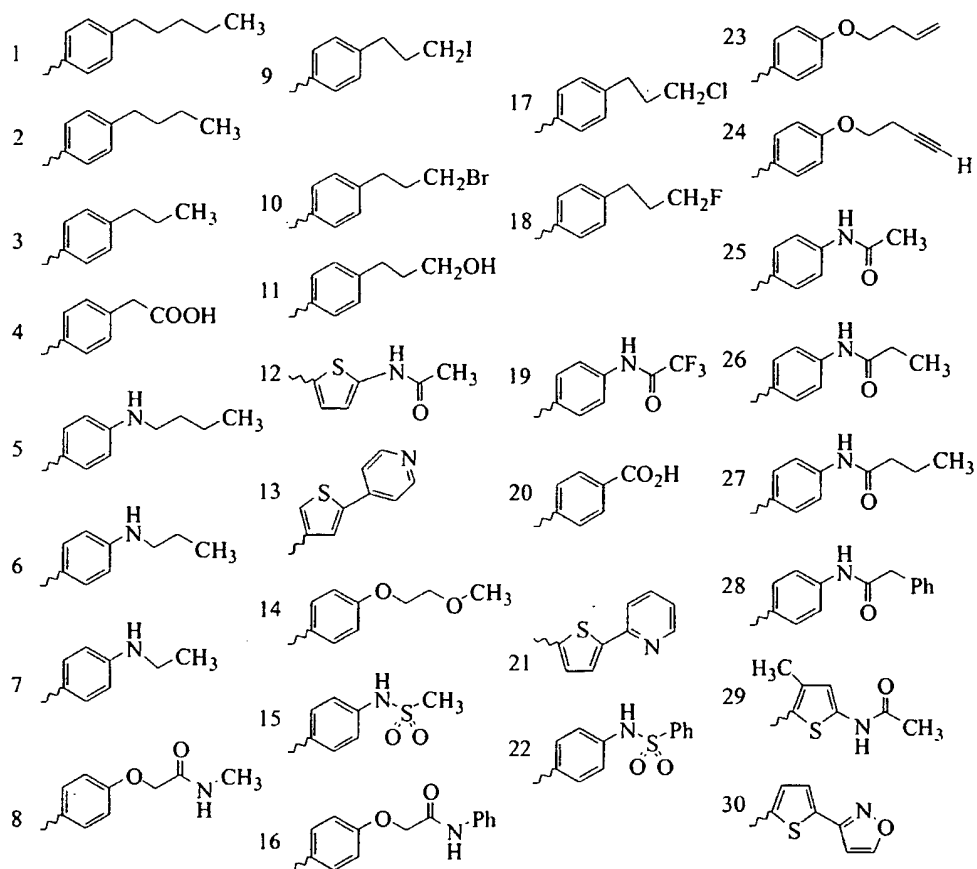
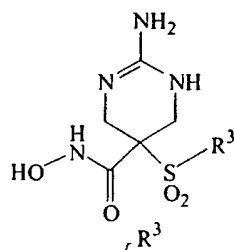
Table 40

Table 41

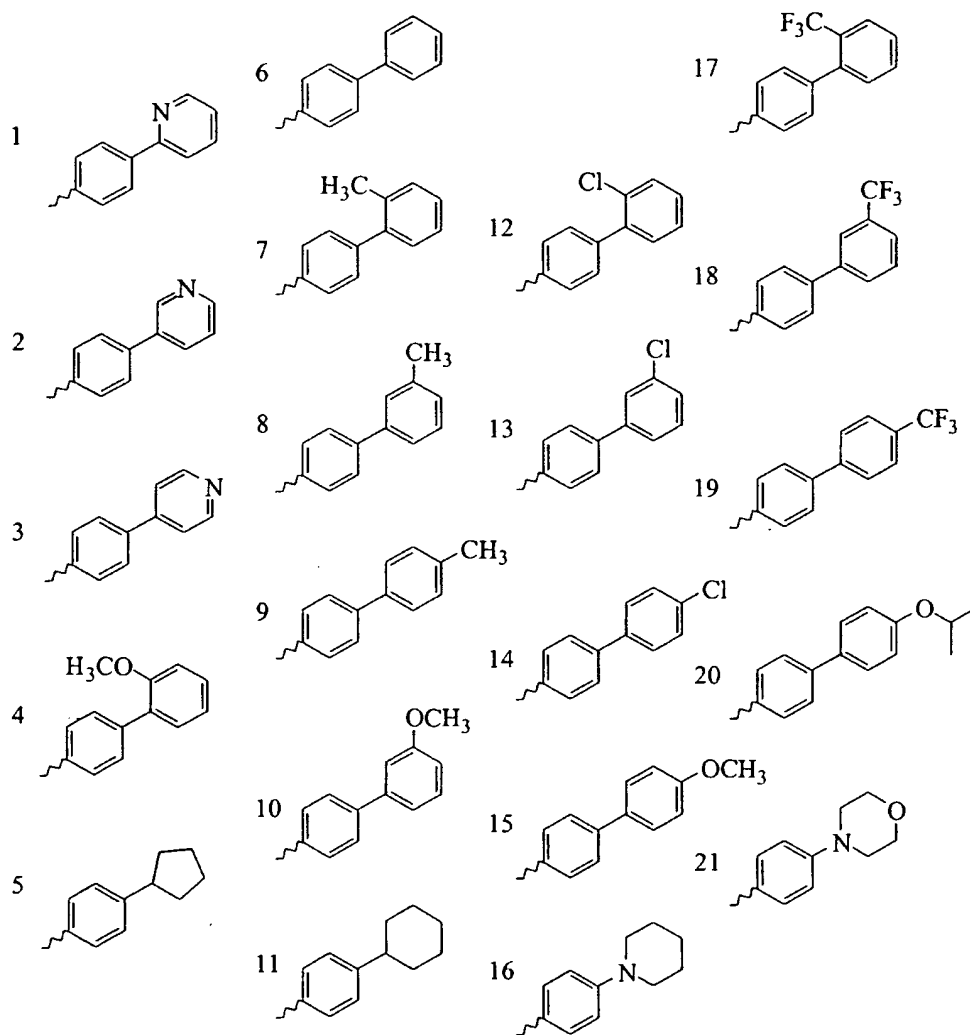
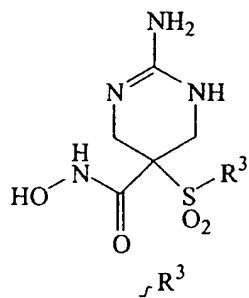


Table 42

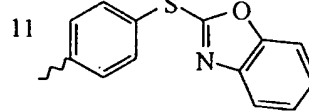
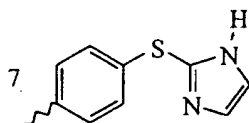
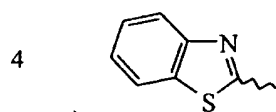
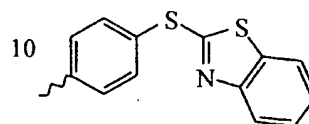
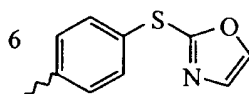
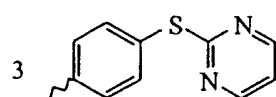
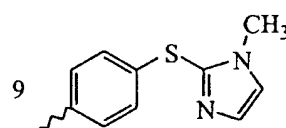
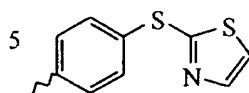
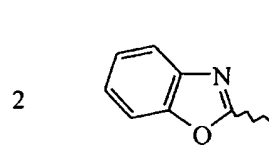
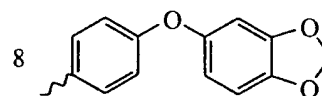
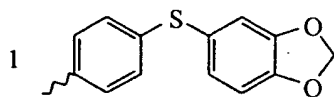
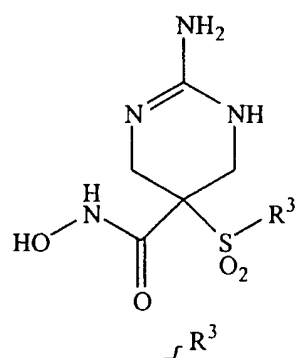
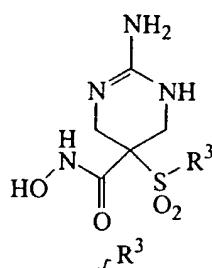


Table 43



1	8	15
2	9	16
3	10	17
4	11	18
5	12	19
6	13	20
7	14	21

Table 44

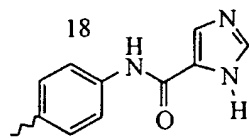
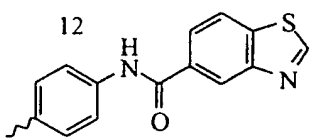
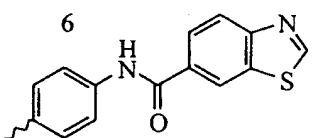
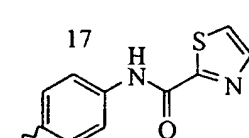
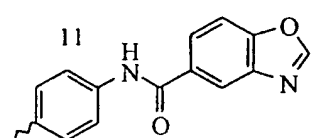
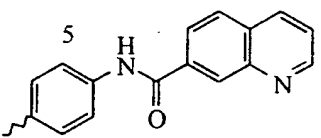
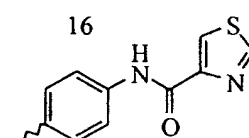
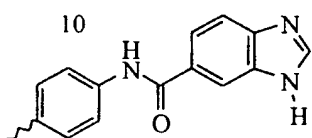
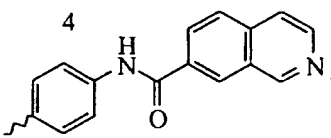
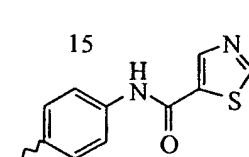
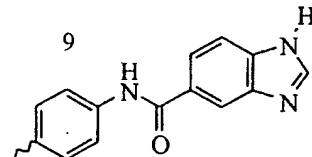
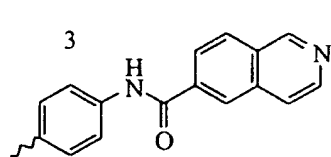
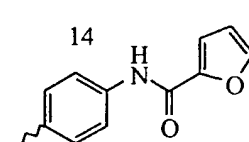
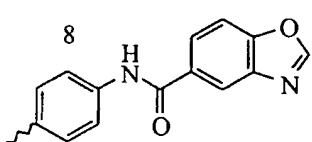
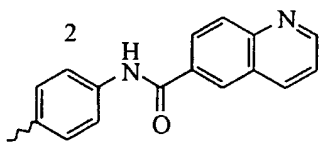
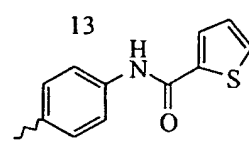
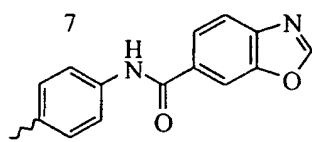
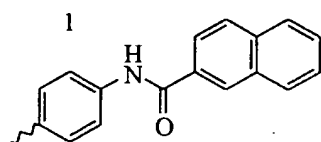
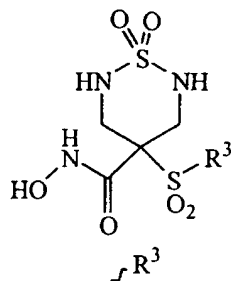


Table 45

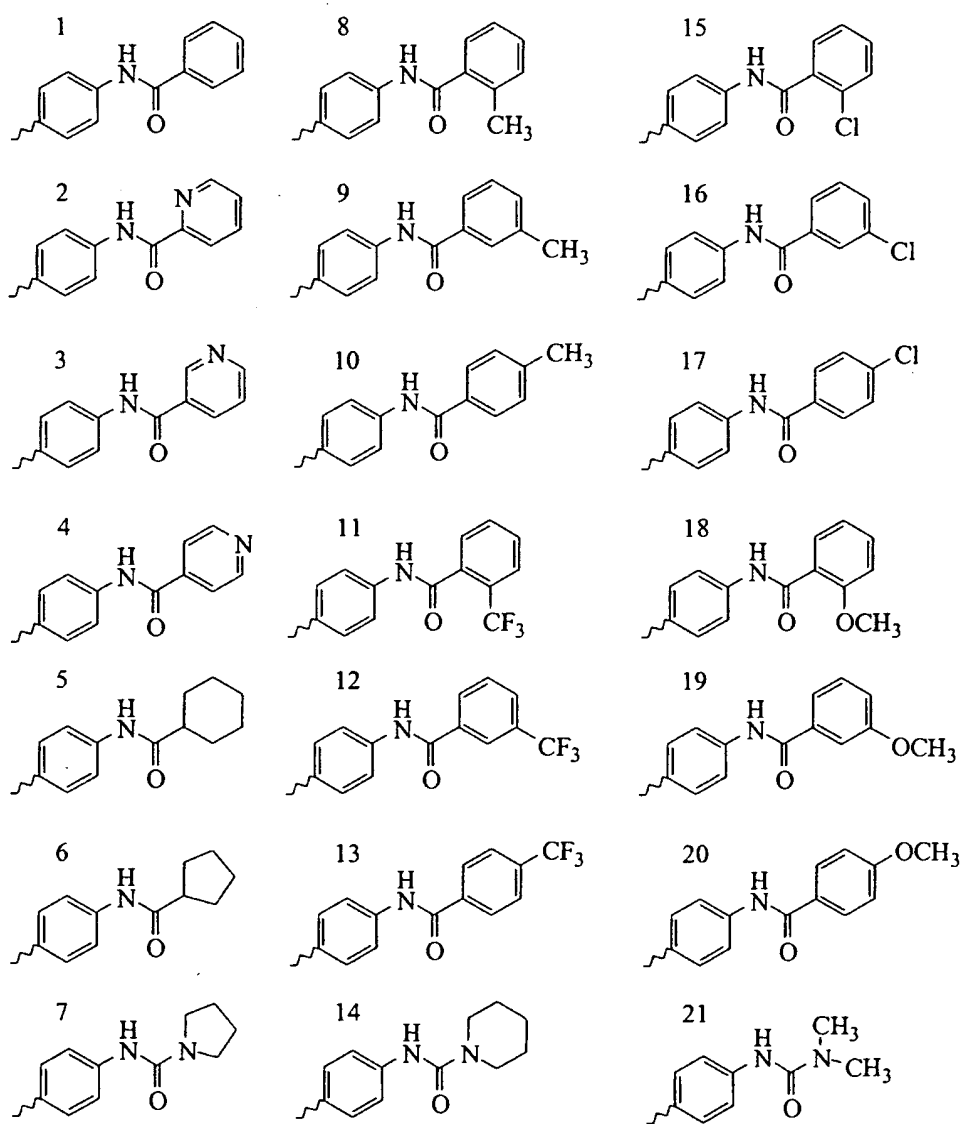
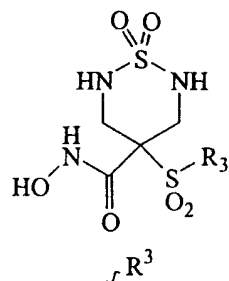


Table 46

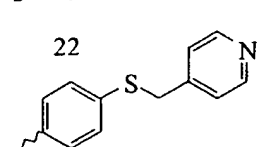
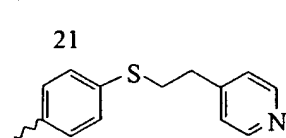
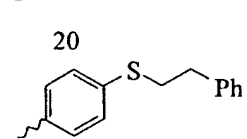
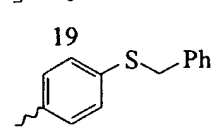
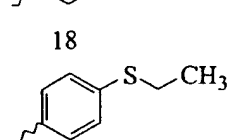
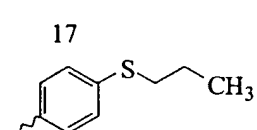
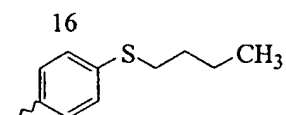
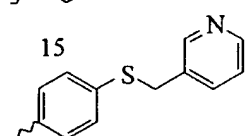
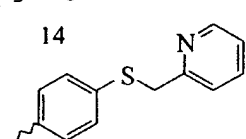
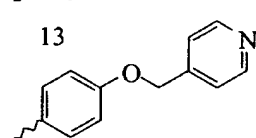
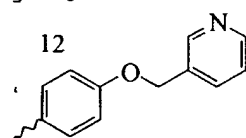
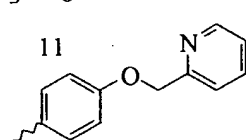
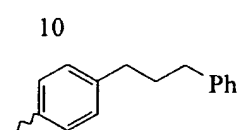
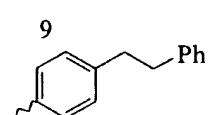
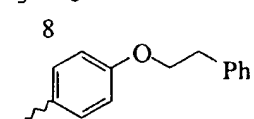
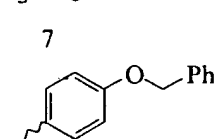
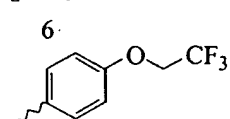
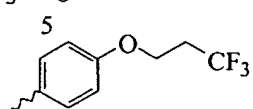
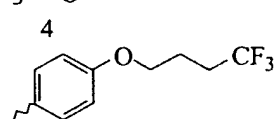
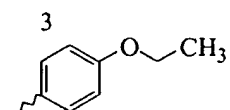
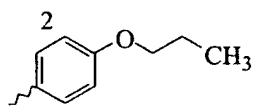
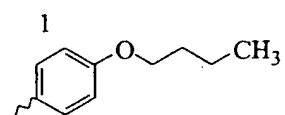
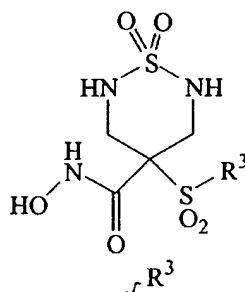


Table 47

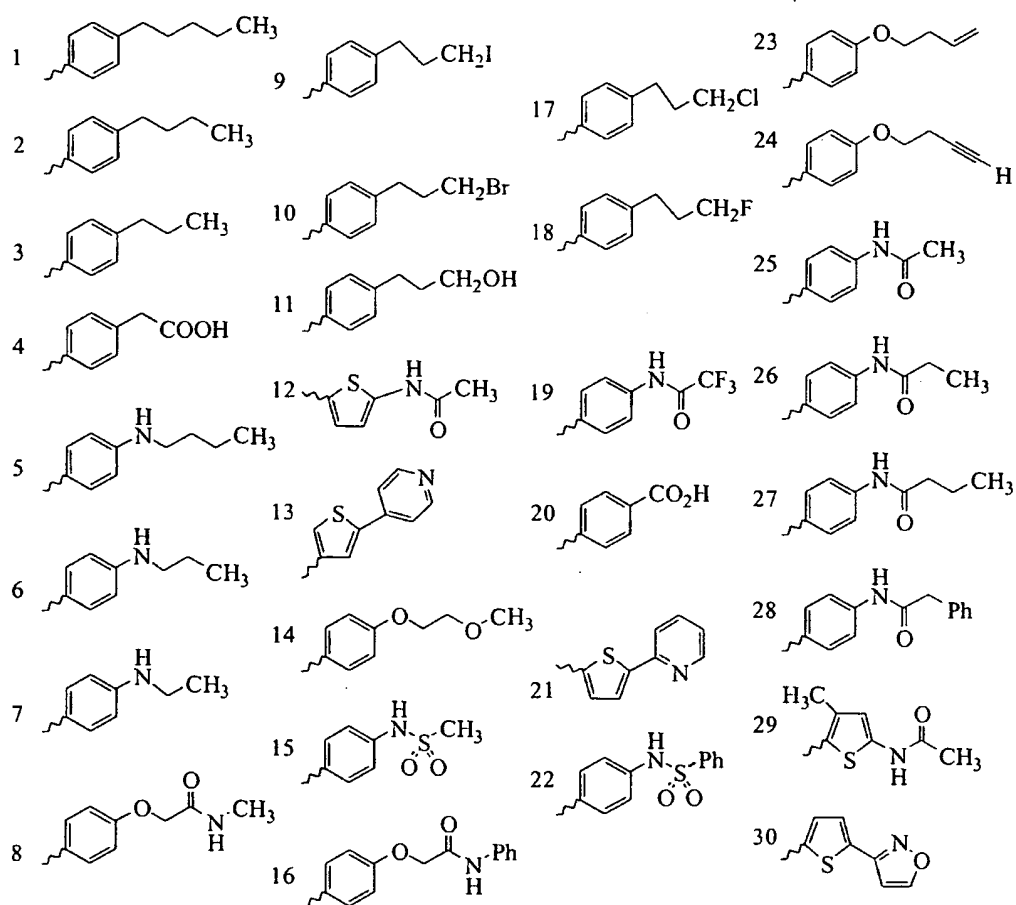
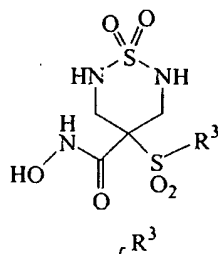


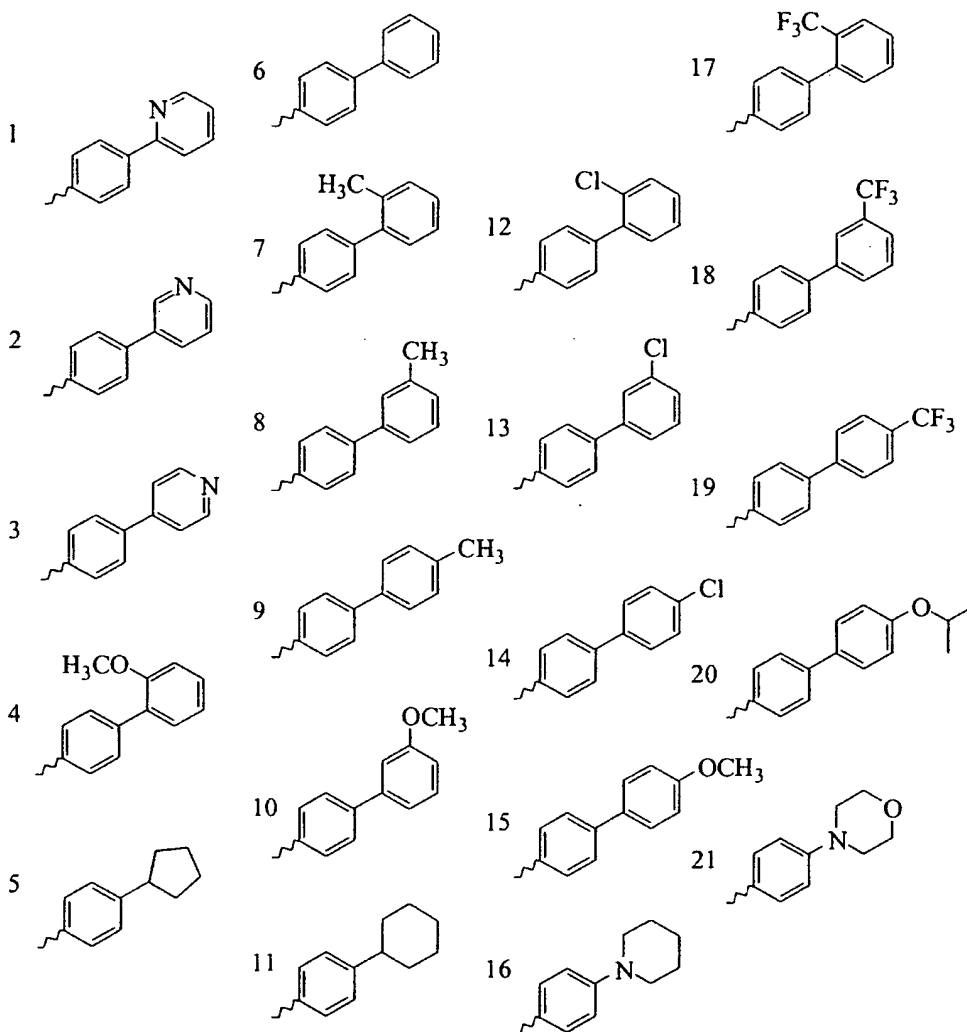
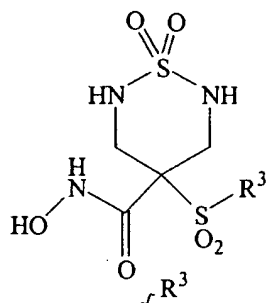
Table 48

Table 49

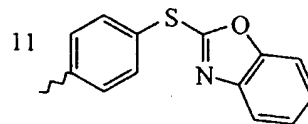
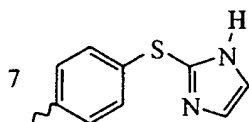
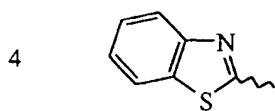
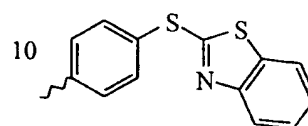
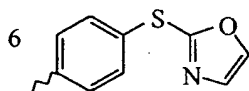
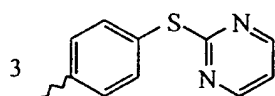
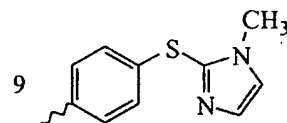
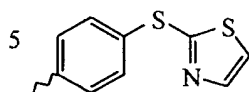
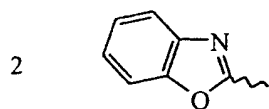
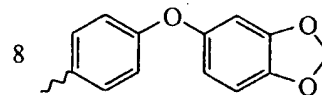
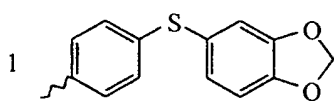
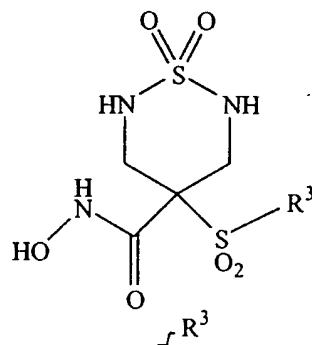
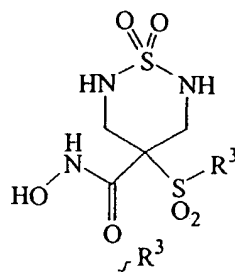


Table 50



1 	8 	15
2 	9 	16
3 	10 	17
4 	11 	18
5 	12 	19
6 	13 	20
7 	14 	21

Table 51

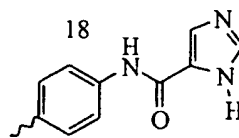
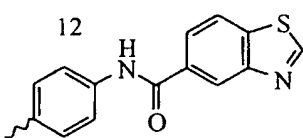
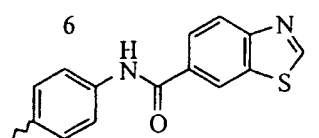
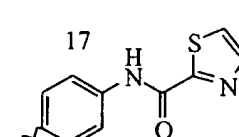
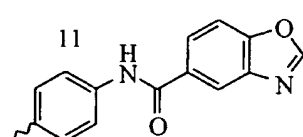
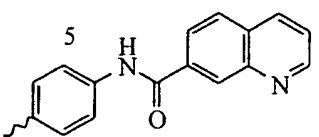
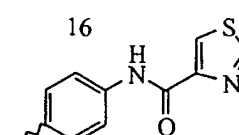
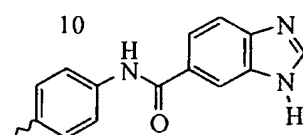
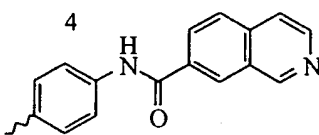
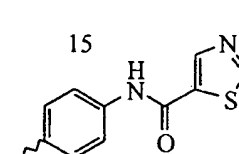
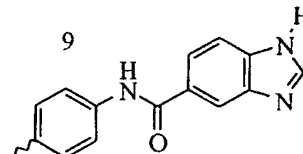
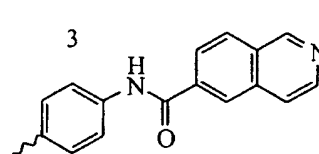
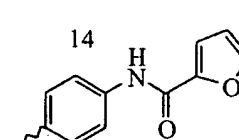
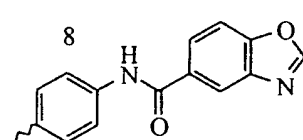
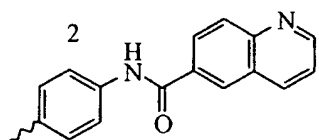
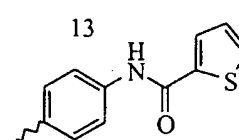
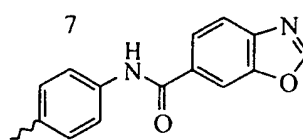
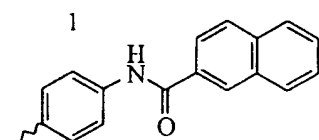
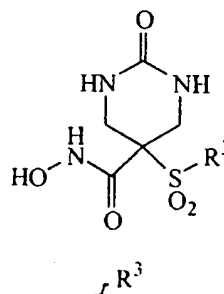


Table 52

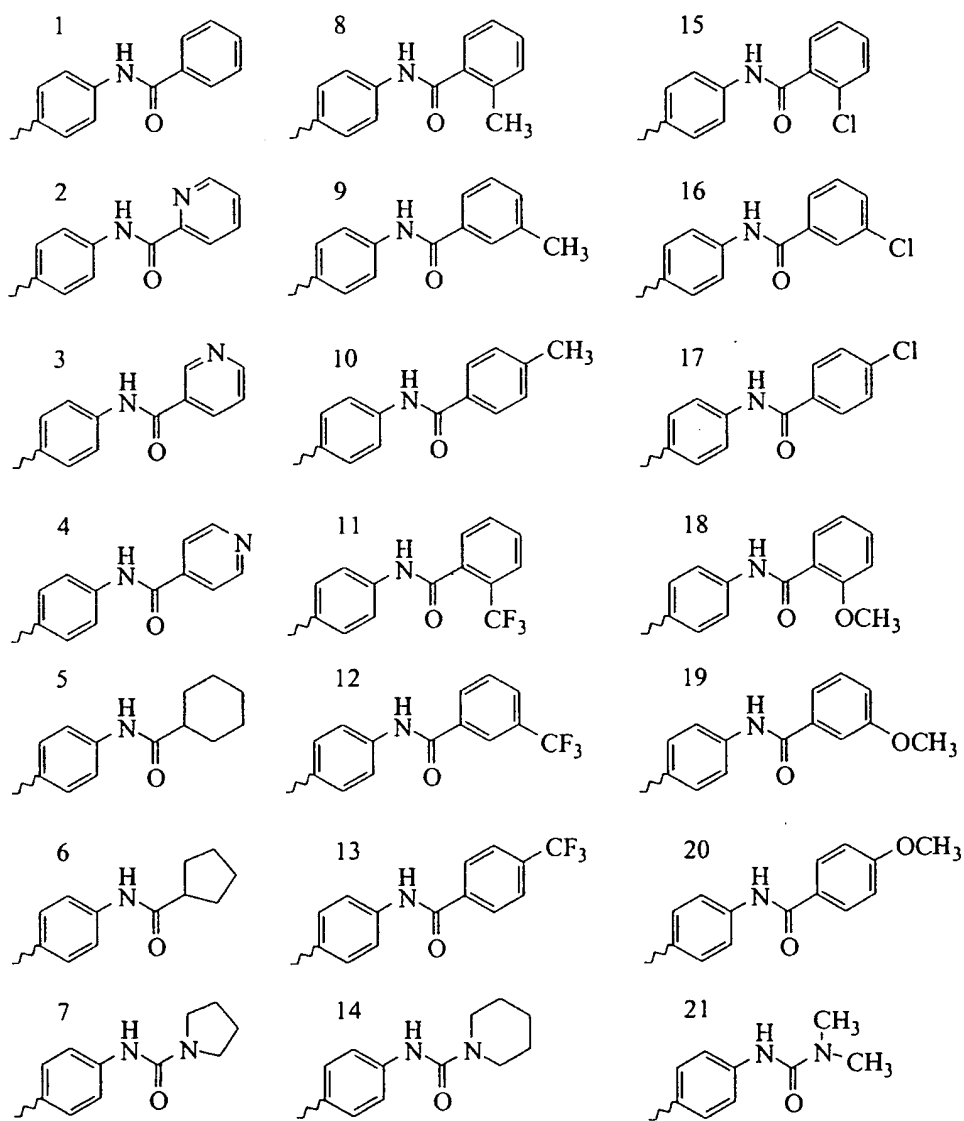
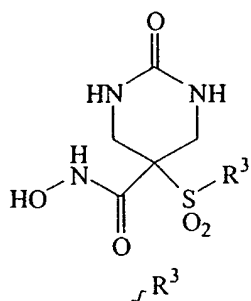


Table 53

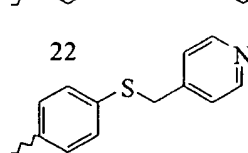
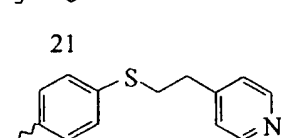
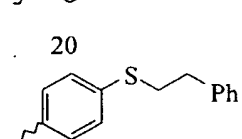
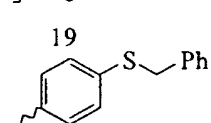
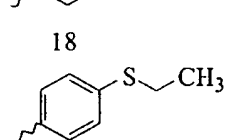
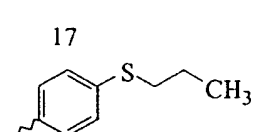
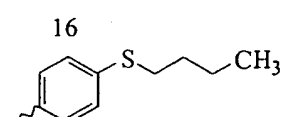
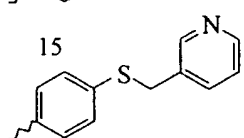
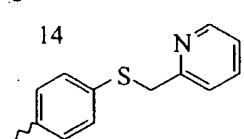
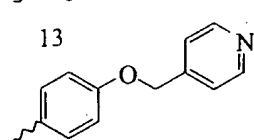
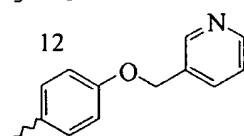
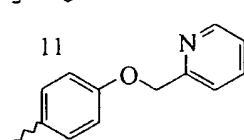
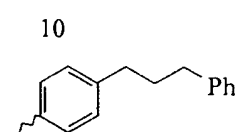
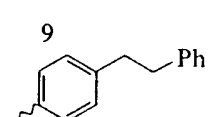
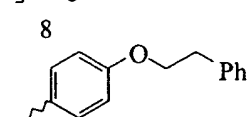
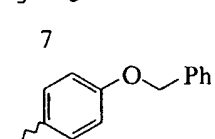
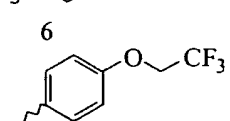
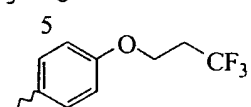
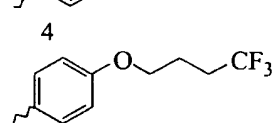
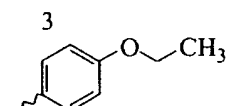
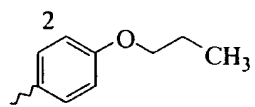
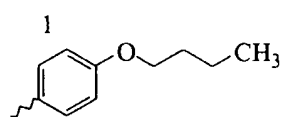
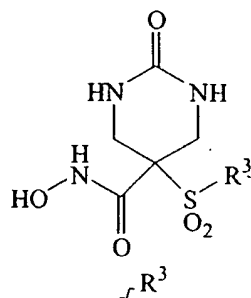


Table 54

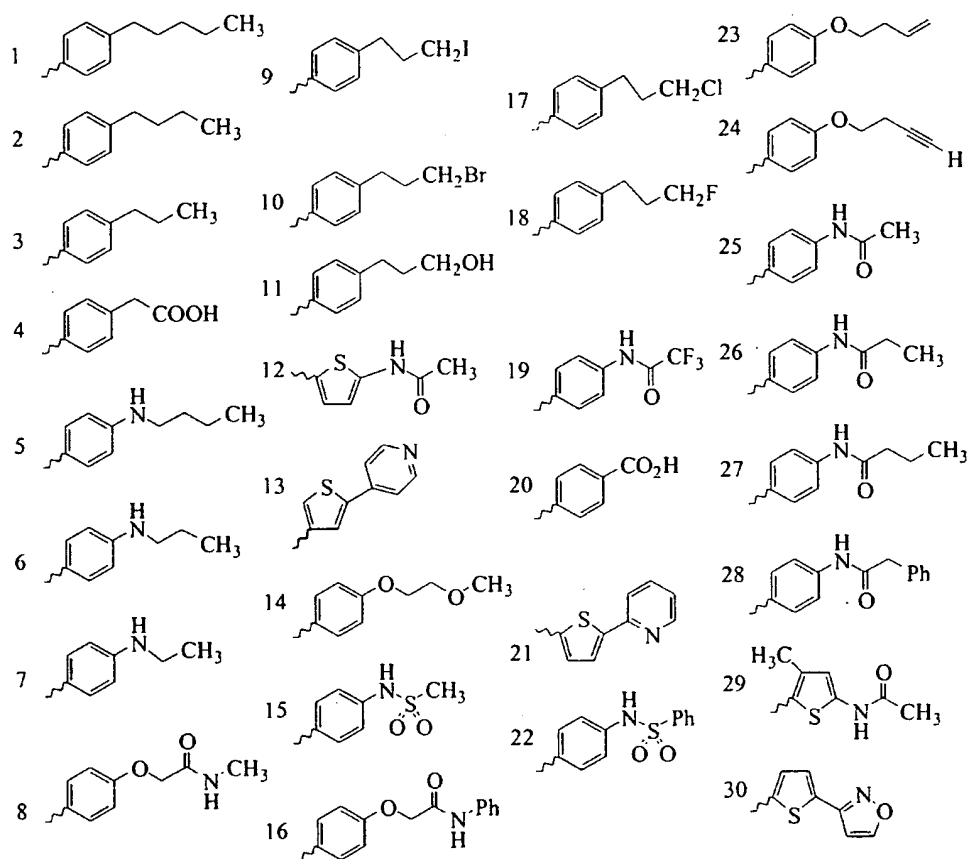
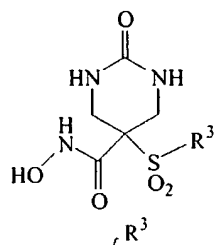


Table 55

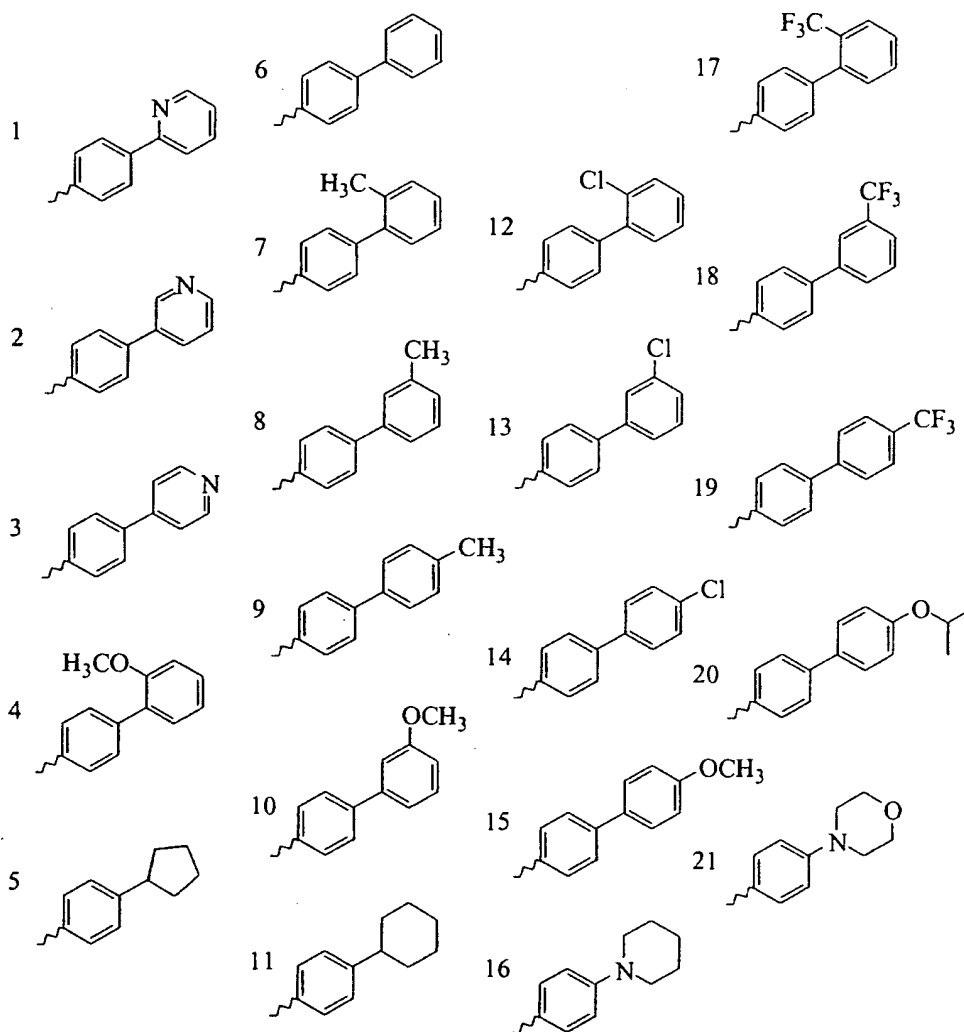
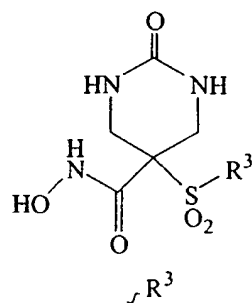


Table 56

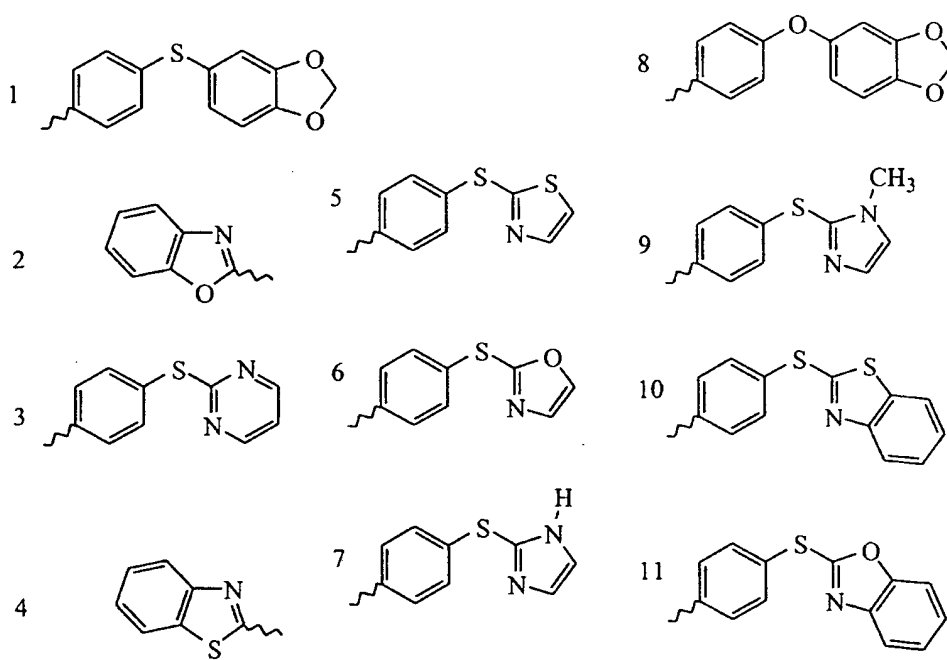
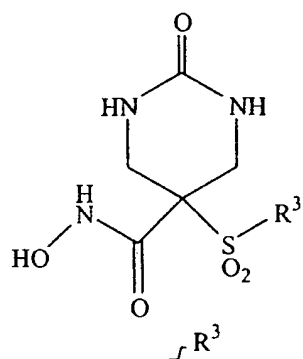
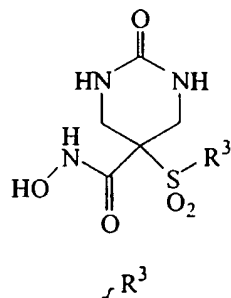


Table 57



1 	8 	15
2 	9 	16
3 	10 	17
4 	11 	18
5 	12 	19
6 	13 	20
7 	14 	21

Table 58

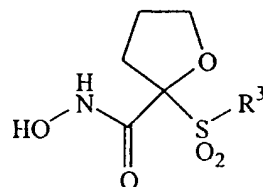
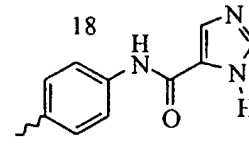
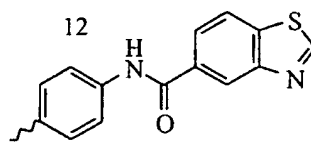
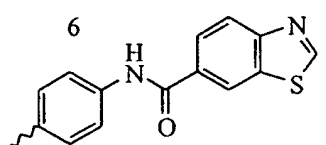
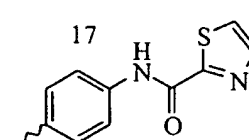
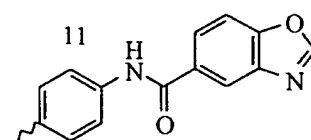
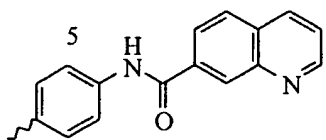
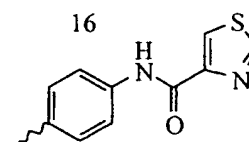
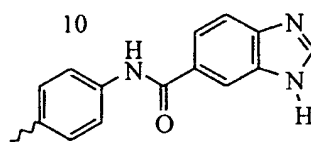
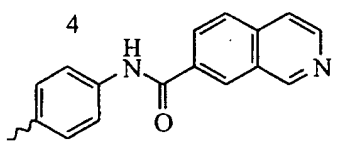
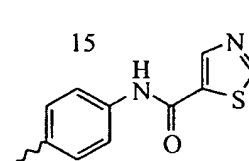
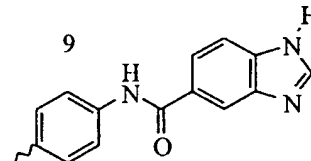
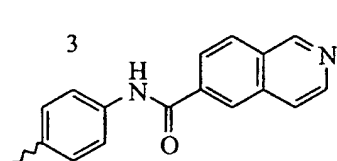
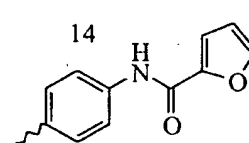
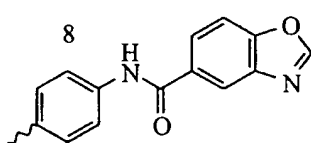
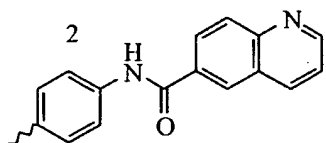
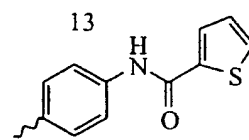
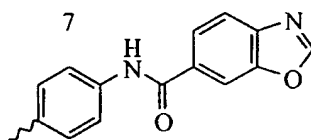
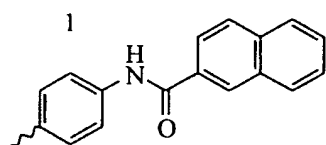
 R^3 

Table 59

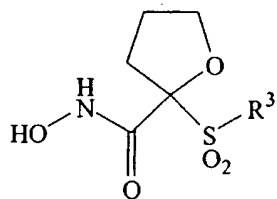
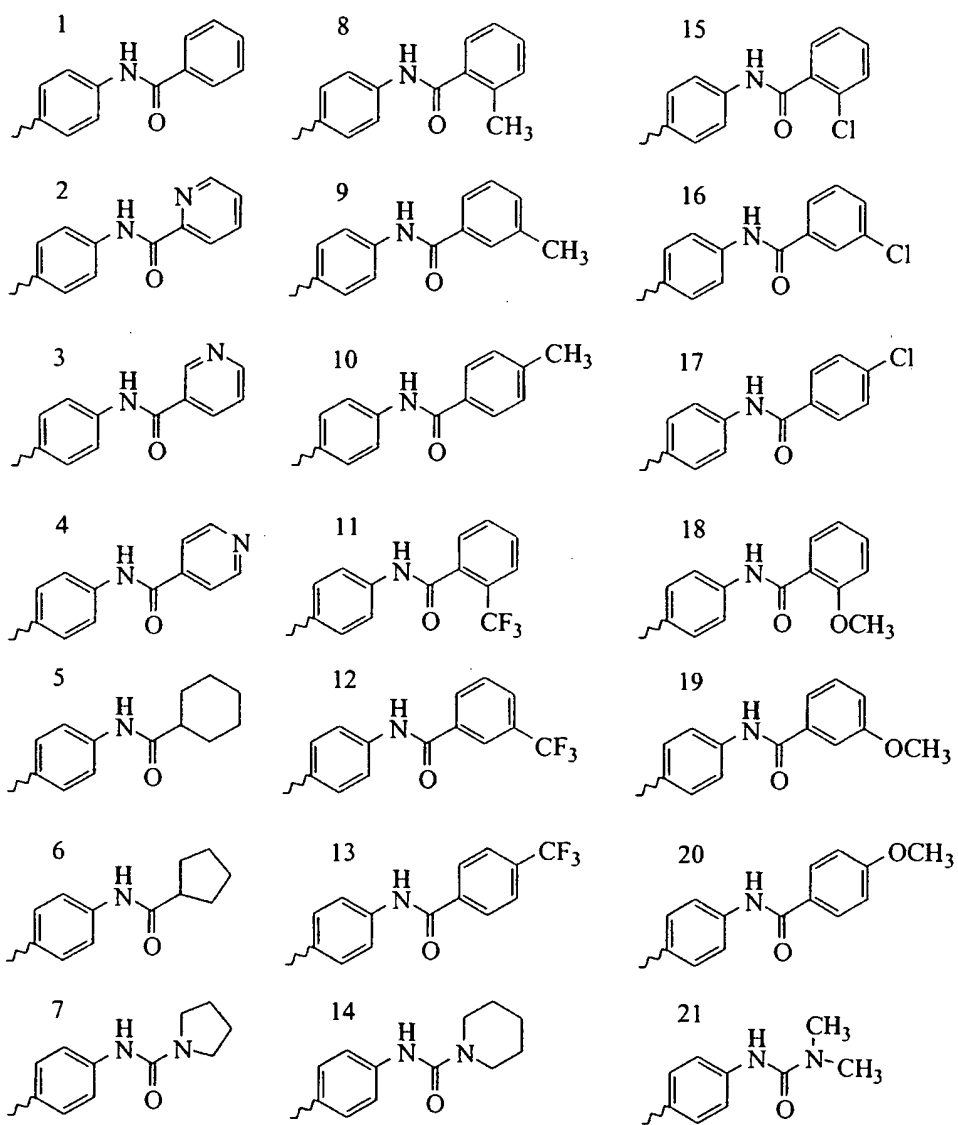
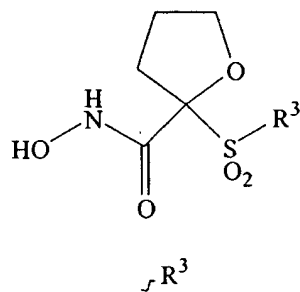
 R^3 

Table 60



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

Table 62

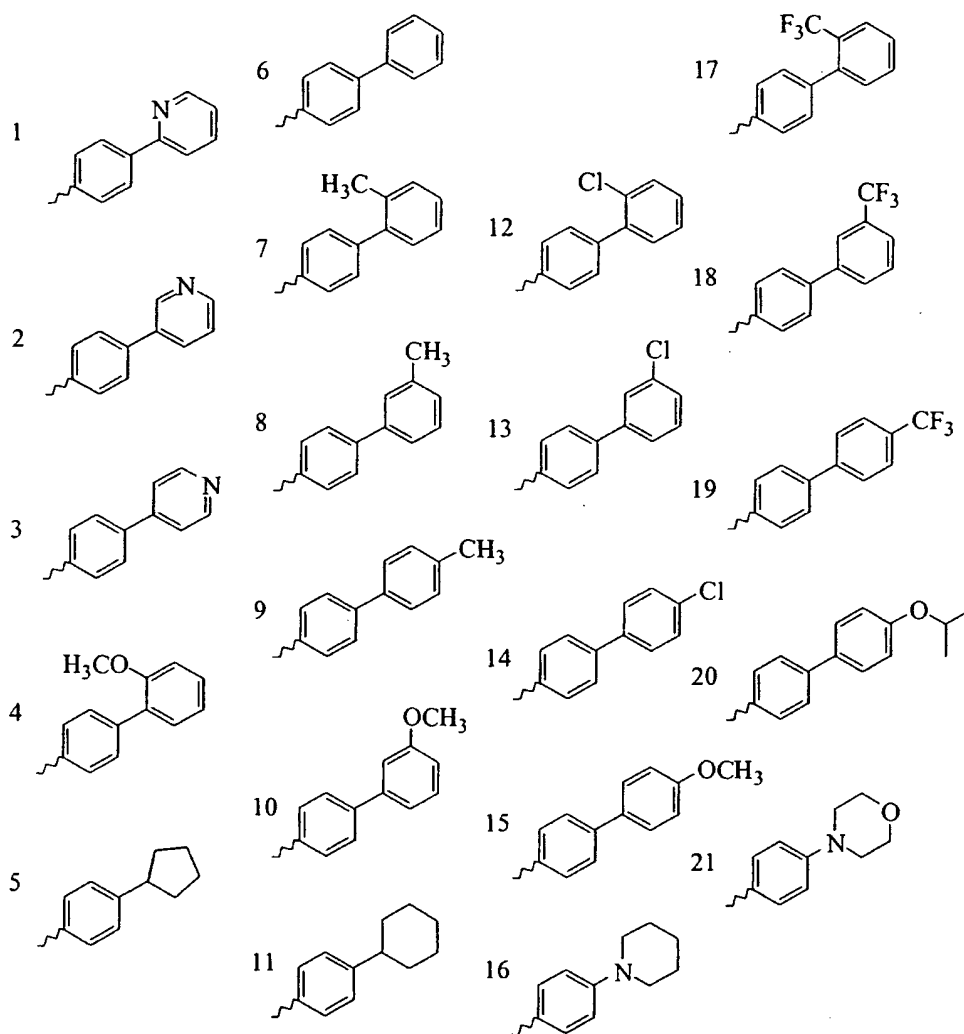
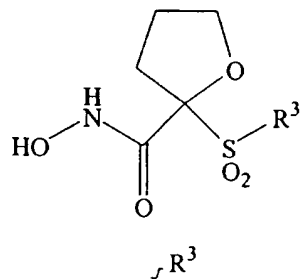


Table 63

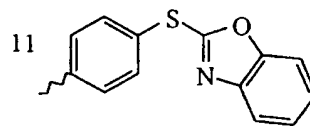
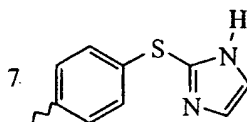
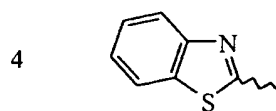
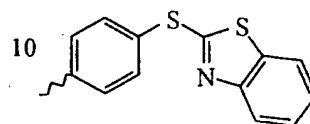
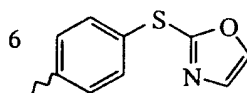
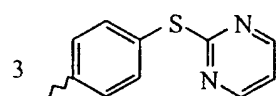
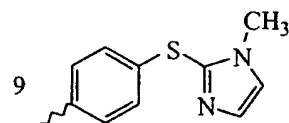
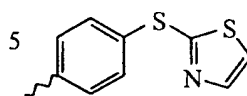
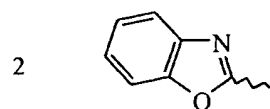
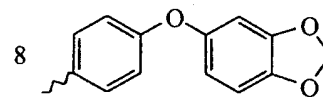
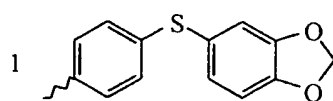
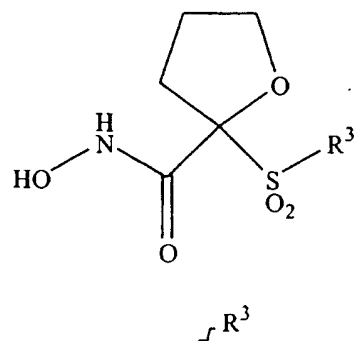
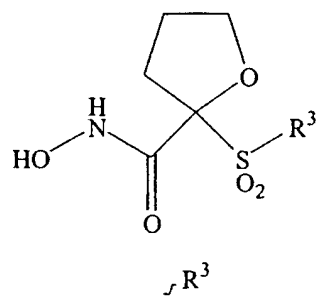


Table 64



1 	8 	15
2 	9 	16
3 	10 	17
4 	11 	18
5 	12 	19
6 	13 	20
7 	14 	21

Table 65

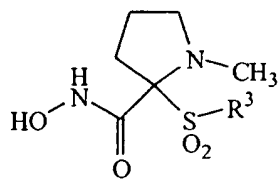
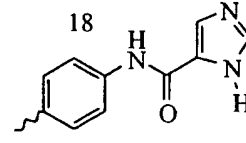
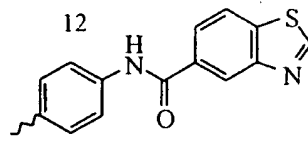
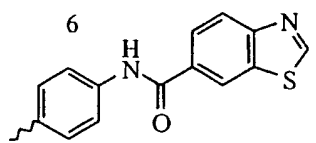
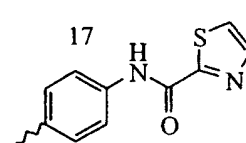
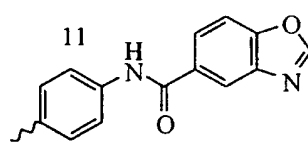
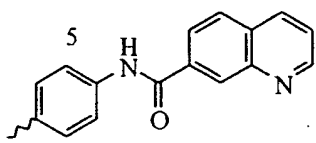
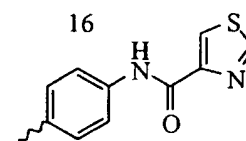
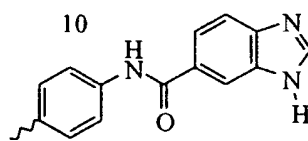
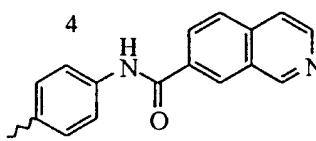
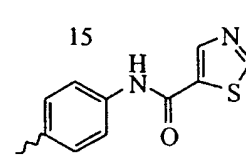
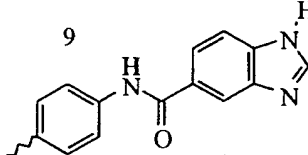
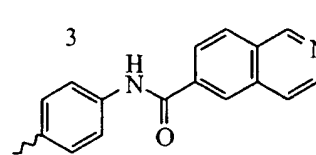
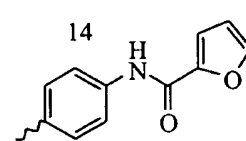
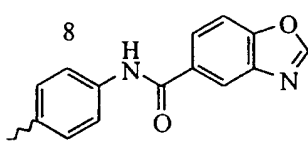
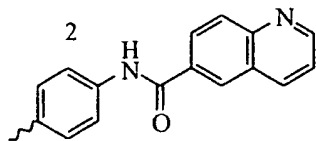
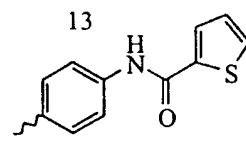
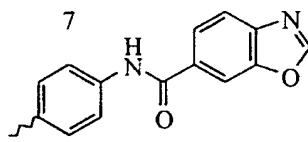
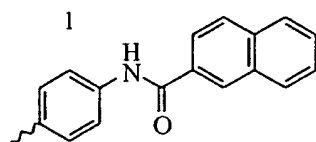
 R^3 

Table 66

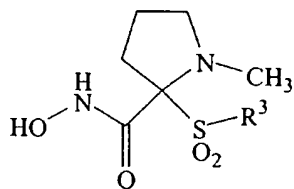
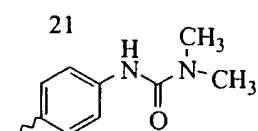
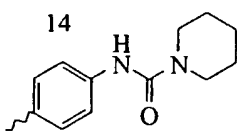
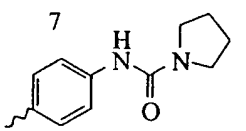
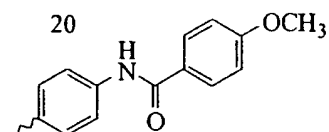
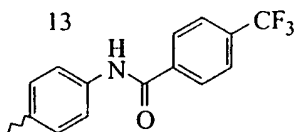
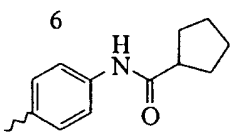
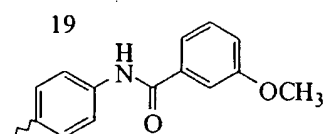
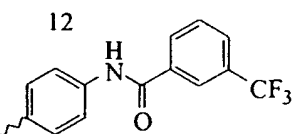
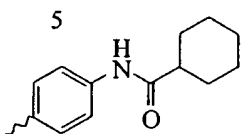
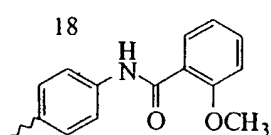
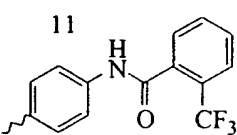
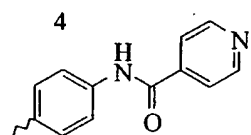
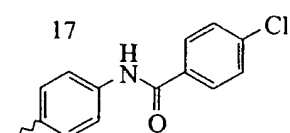
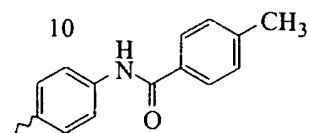
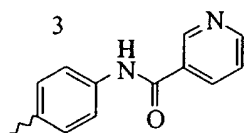
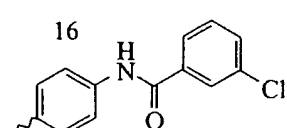
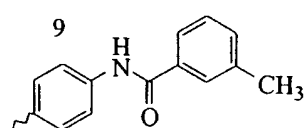
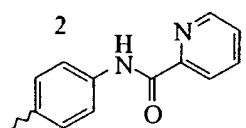
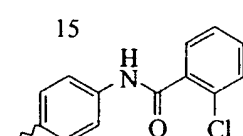
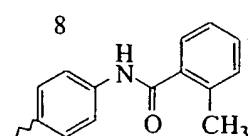
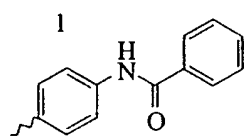
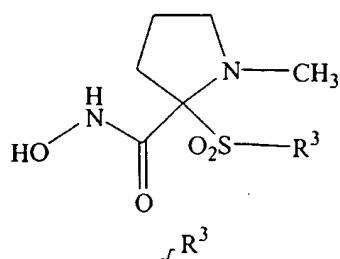
 $\int \mathbb{R}^3$ 

Table 67



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

Table 68

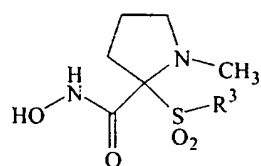
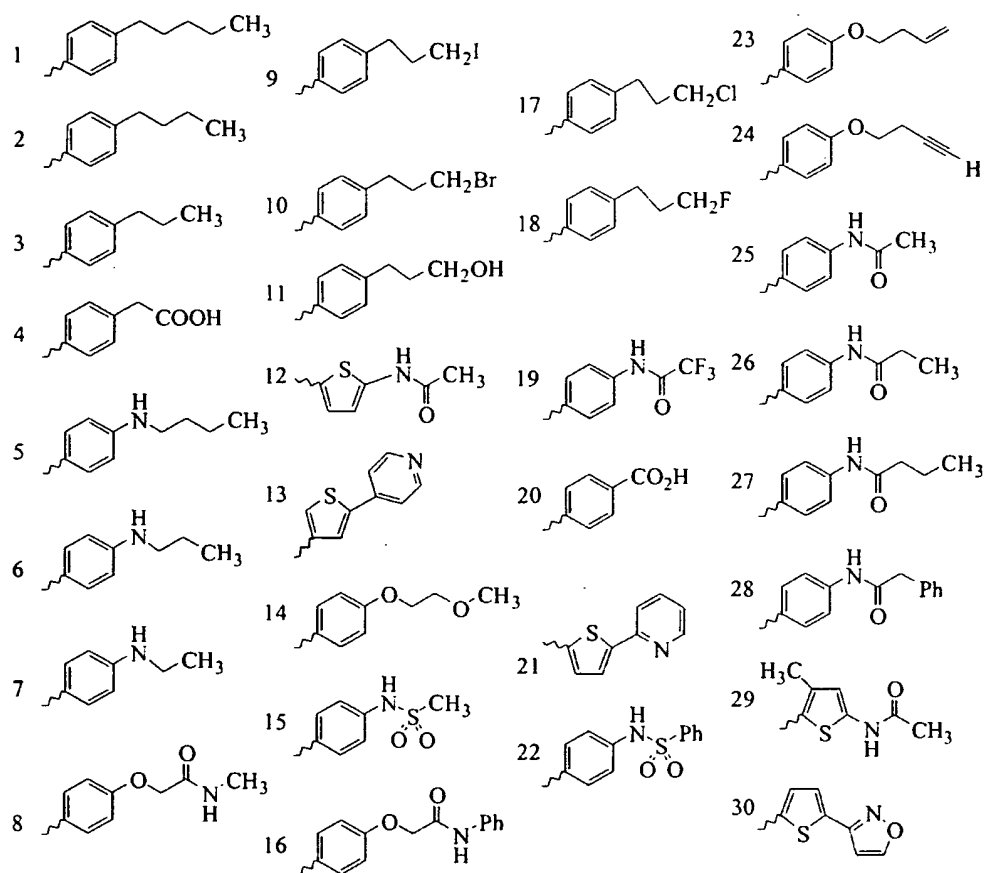
 R^3 

Table 69

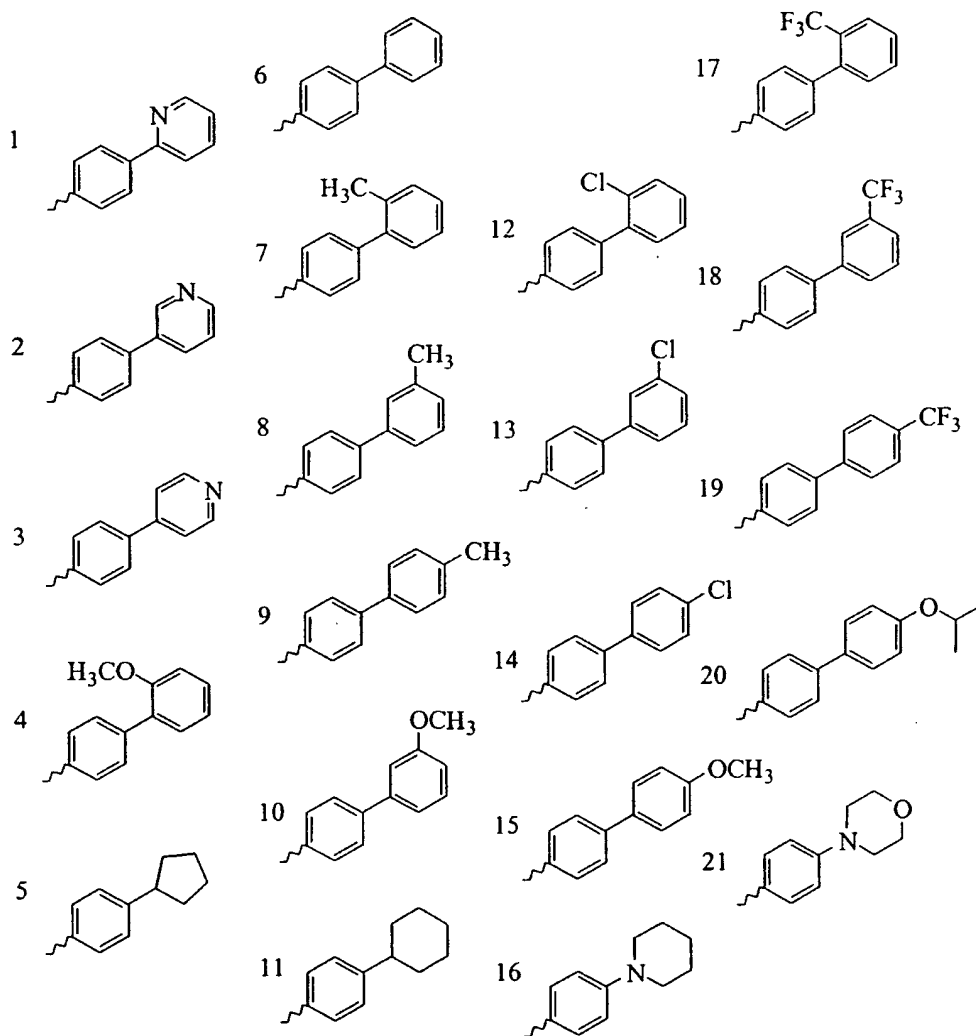
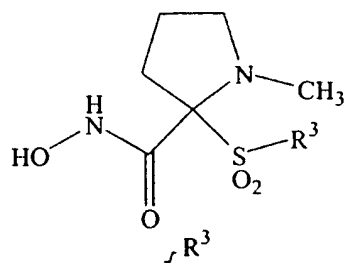


Table 70

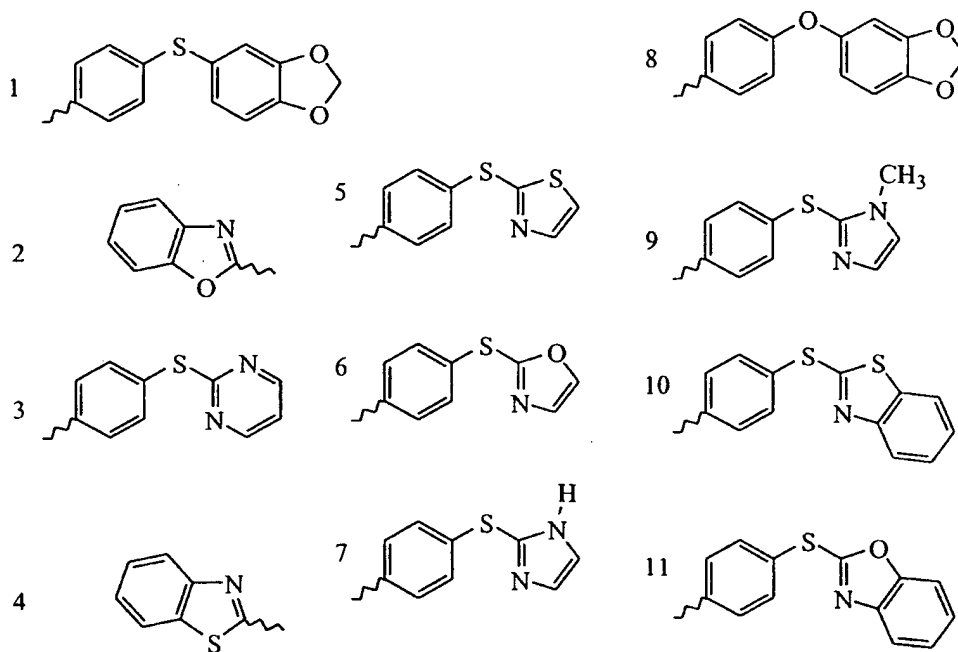
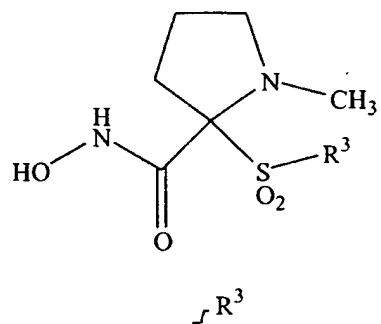
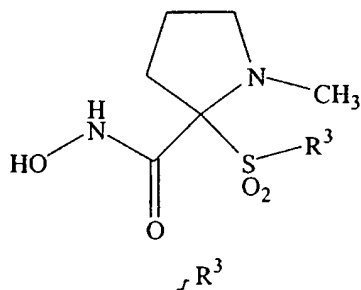


Table 71



1	8	15
2	9	16
3	10	17
4	11	18
5	12	19
6	13	20
7	14	21

Table 72

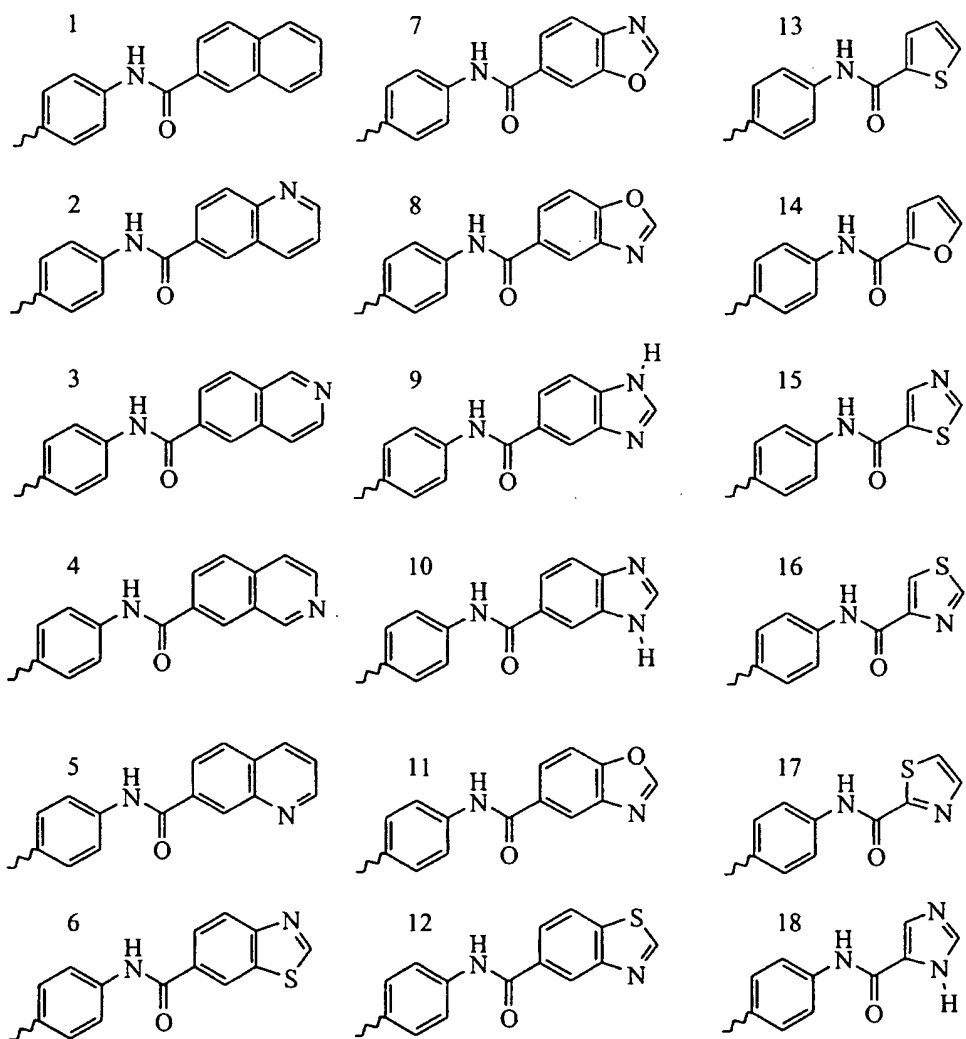
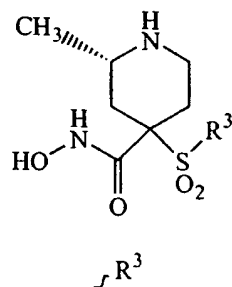


Table 73

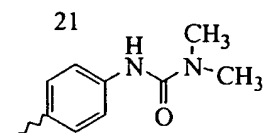
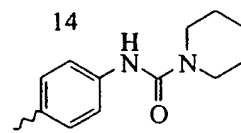
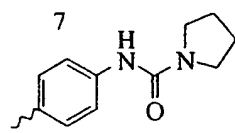
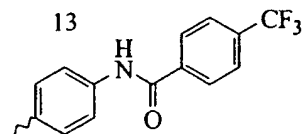
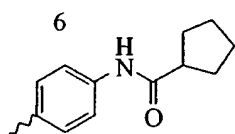
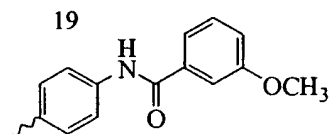
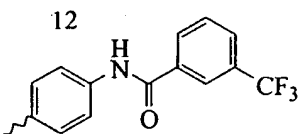
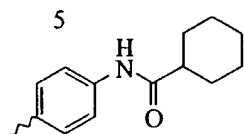
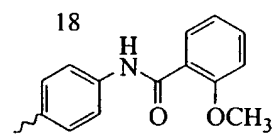
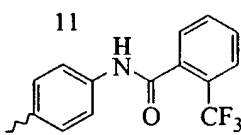
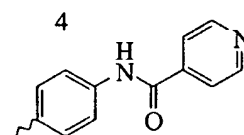
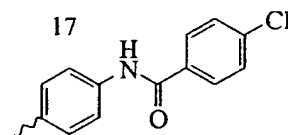
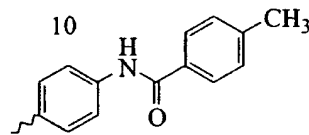
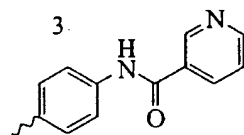
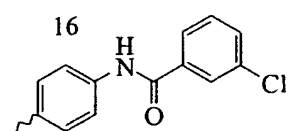
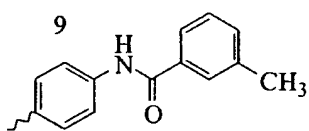
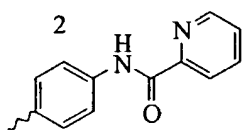
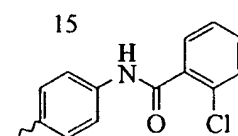
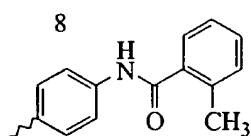
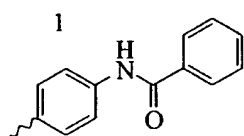
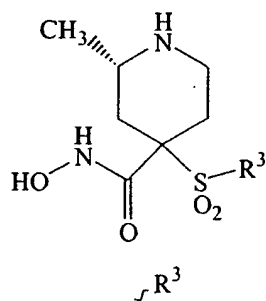
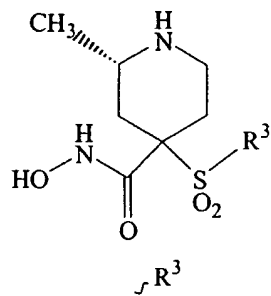


Table 74



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

Table 75

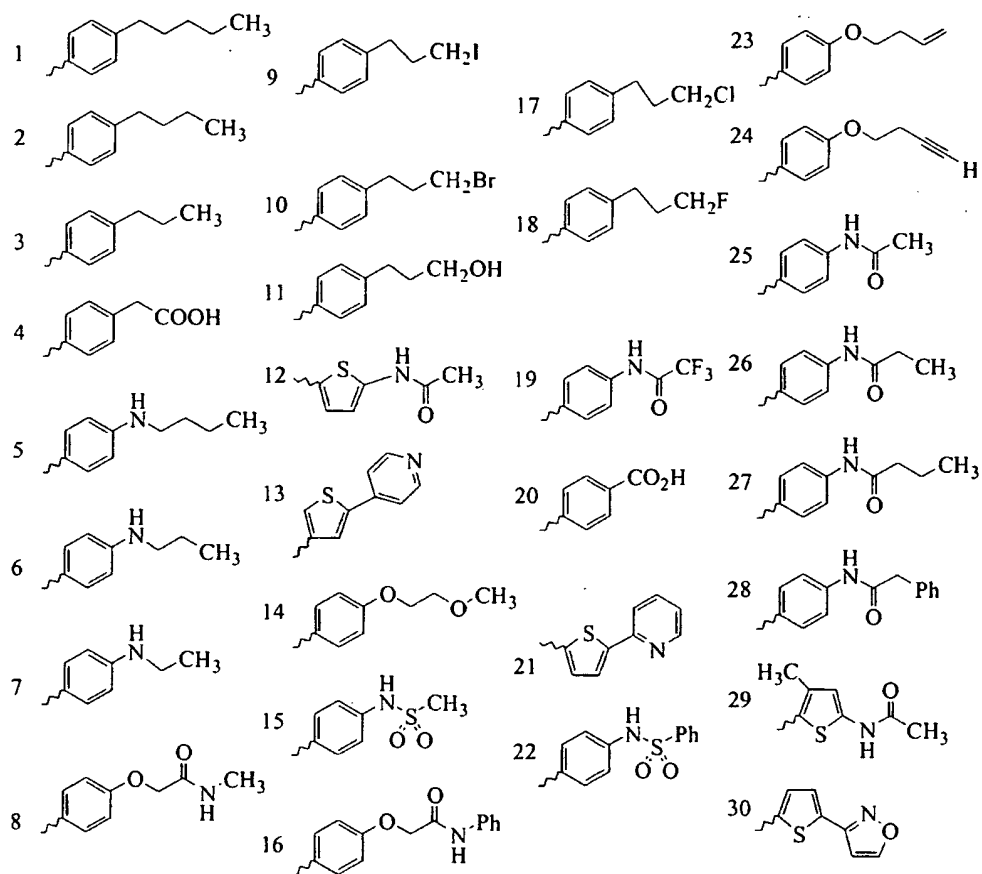
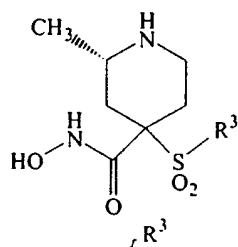


Table 76

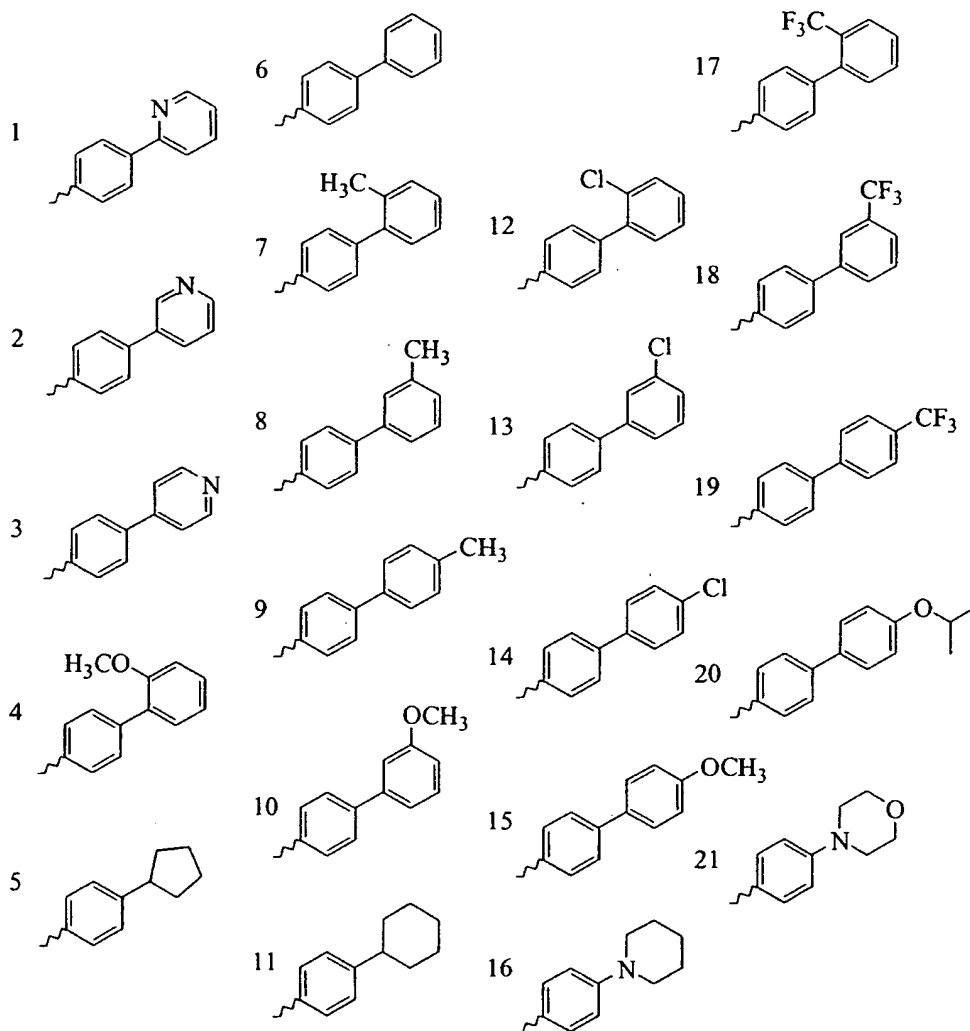
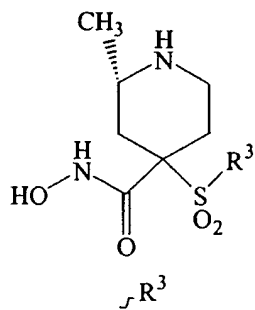


Table 77

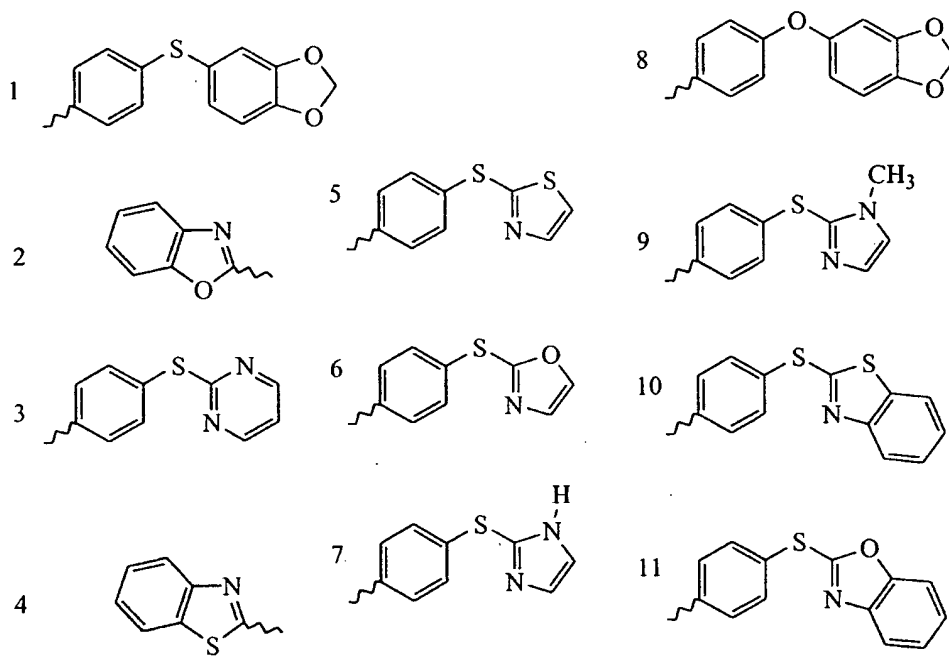
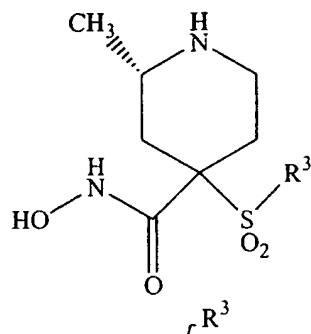
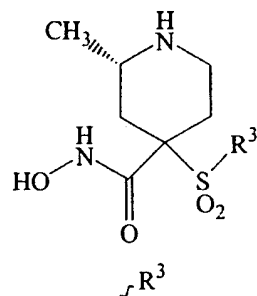


Table 78



1	8	15
2	9	16
3	10	17
4	11	18
5	12	19
6	13	20
7	14	21

Table 79

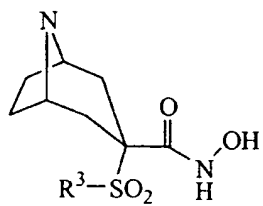
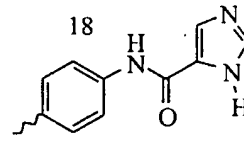
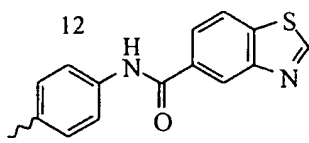
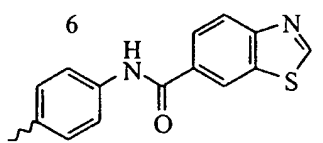
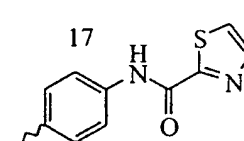
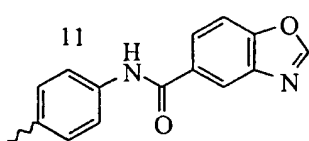
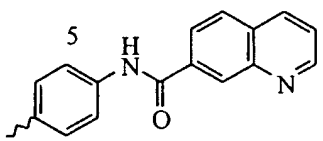
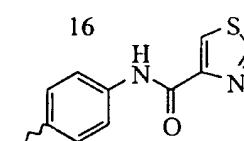
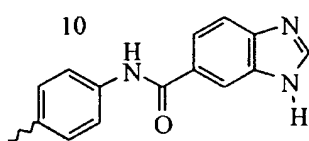
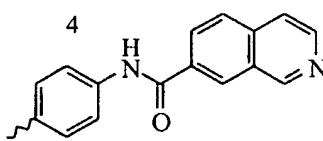
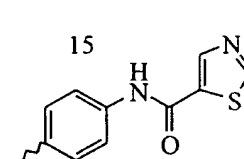
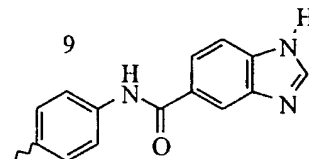
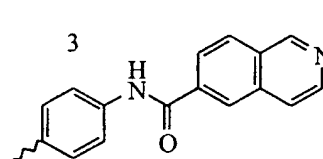
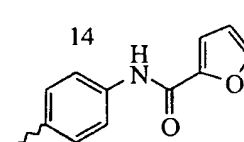
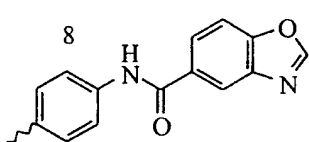
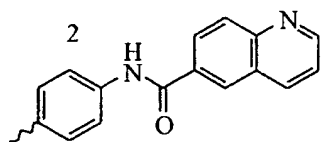
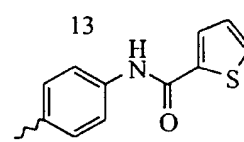
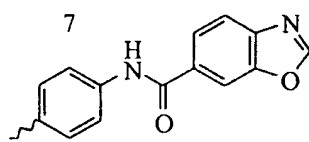
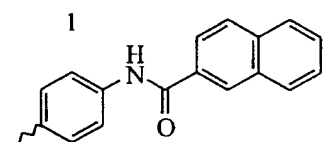
 R^3 

Table 80

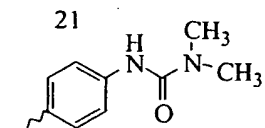
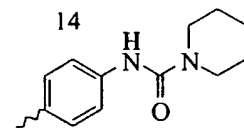
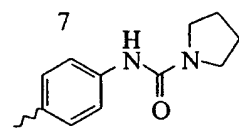
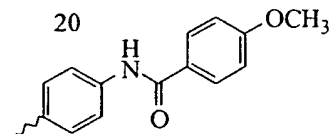
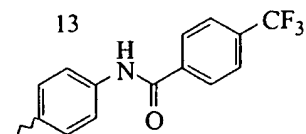
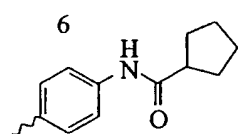
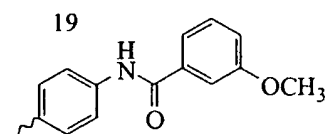
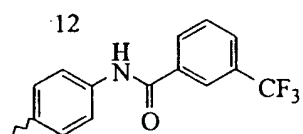
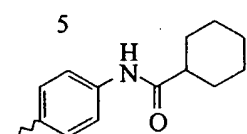
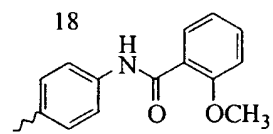
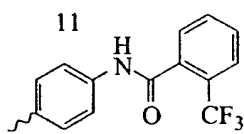
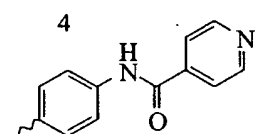
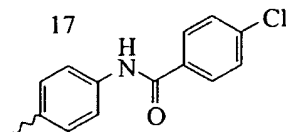
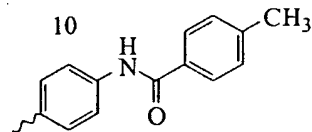
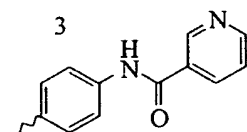
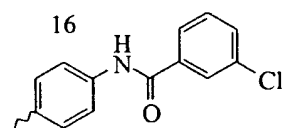
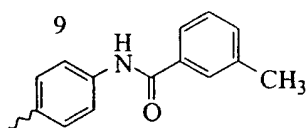
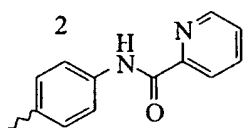
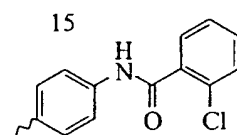
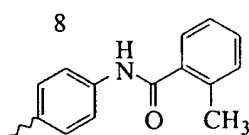
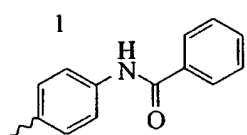
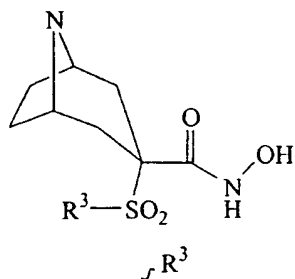
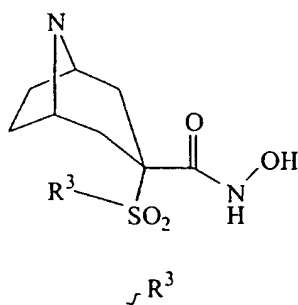


Table 81



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

Table 82

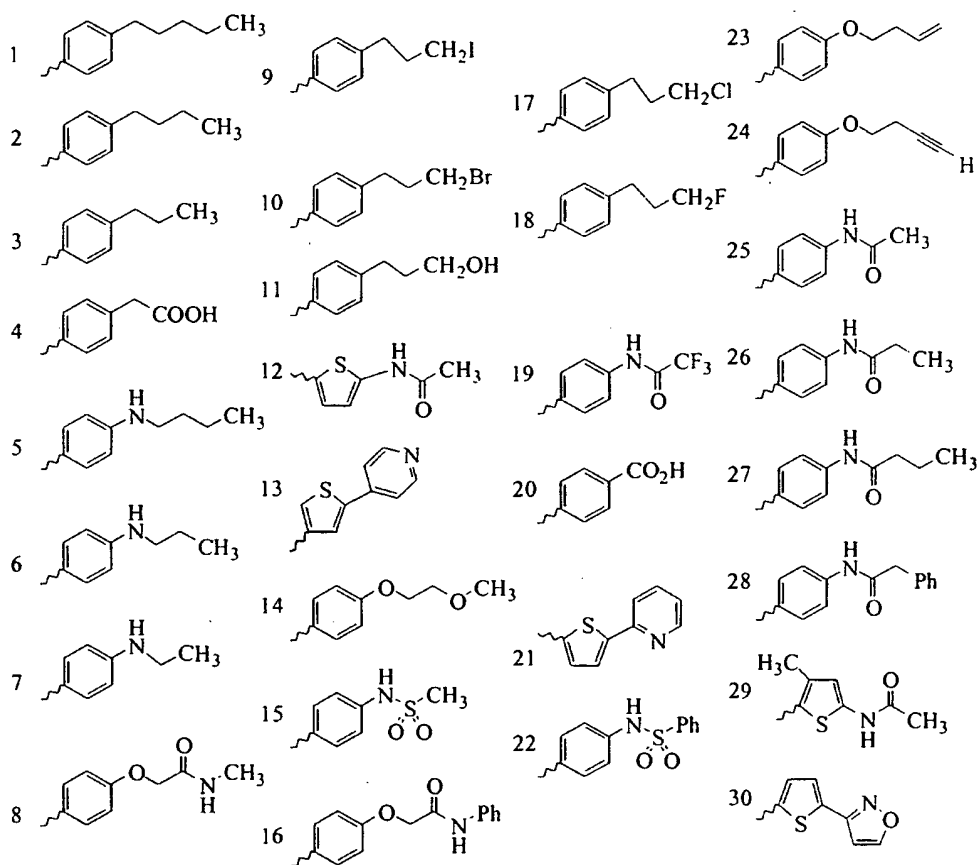
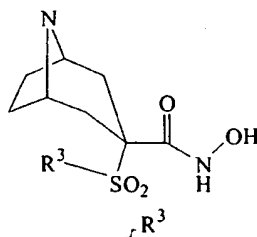


Table 83

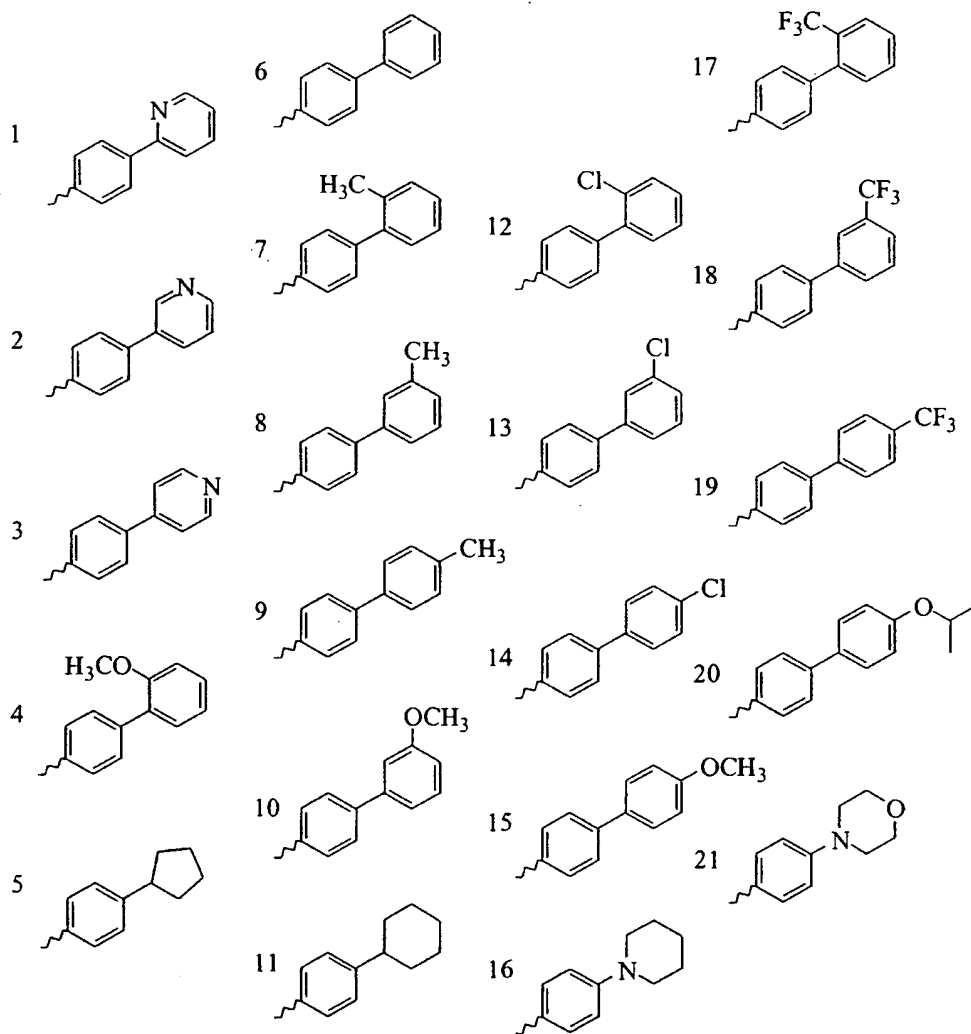
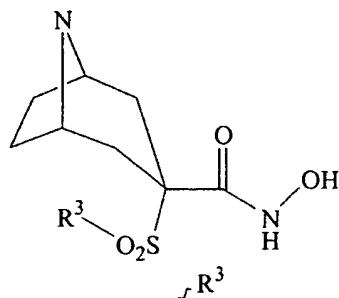


Table 84

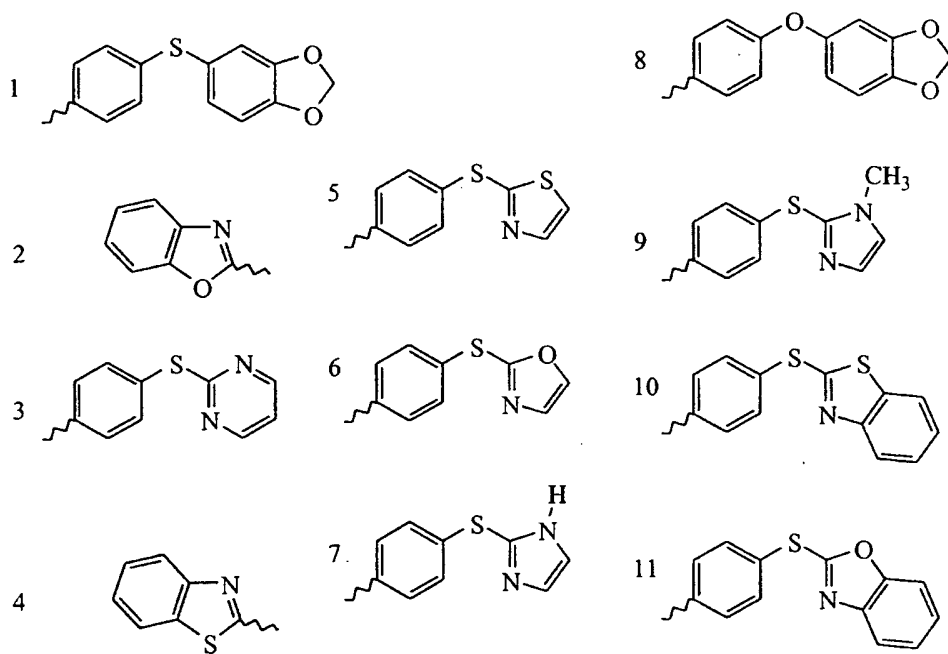
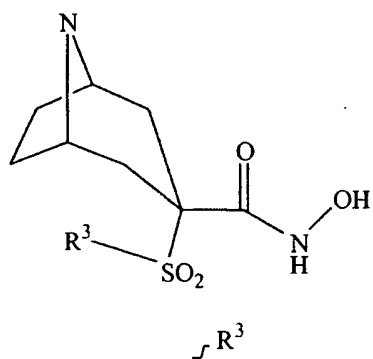
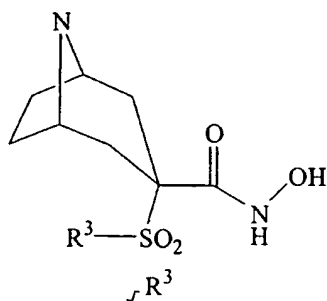


Table 85



1	8	15
2	9	16
3	10	17
4	11	18
5	12	19
6	13	20
7	14	21

Table 86

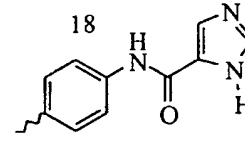
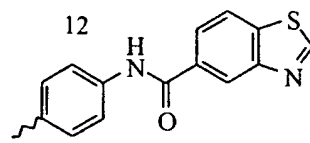
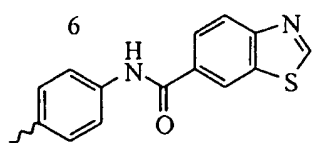
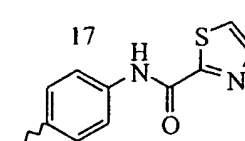
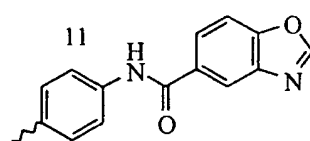
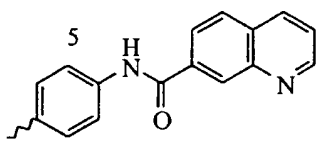
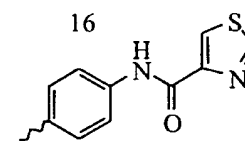
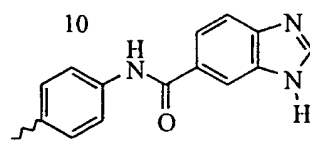
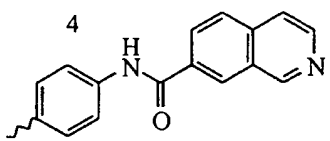
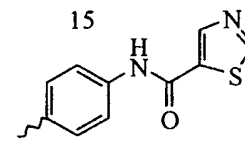
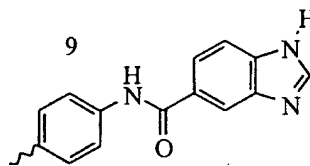
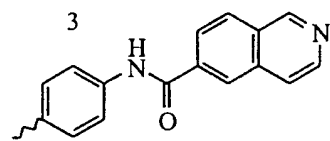
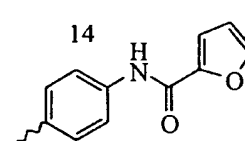
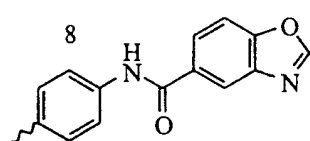
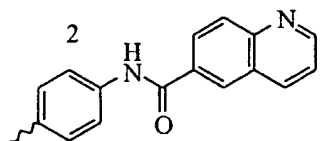
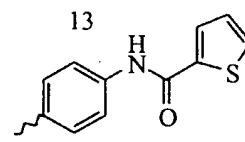
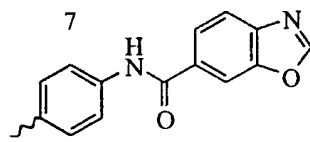
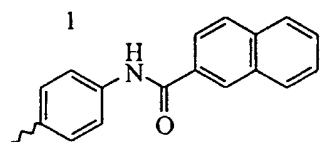
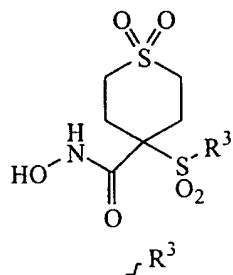


Table 87

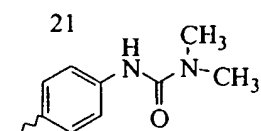
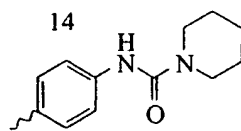
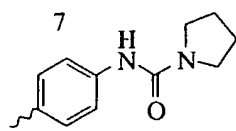
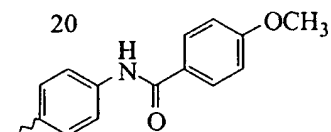
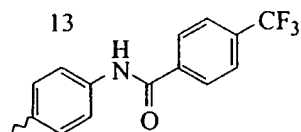
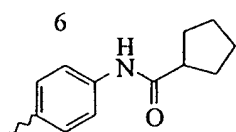
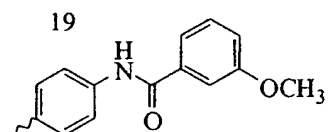
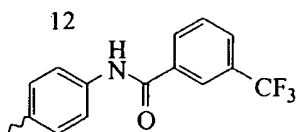
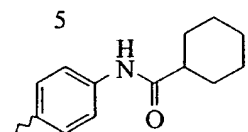
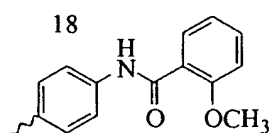
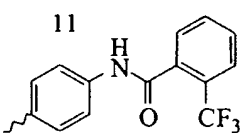
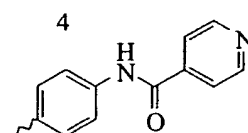
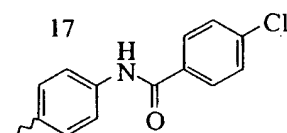
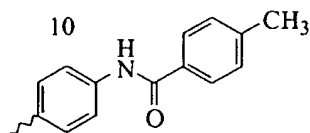
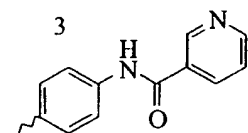
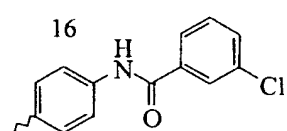
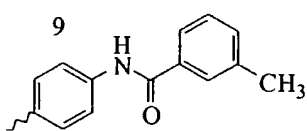
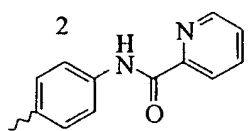
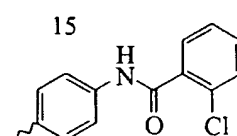
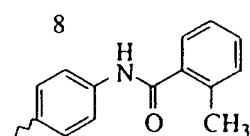
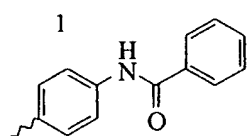
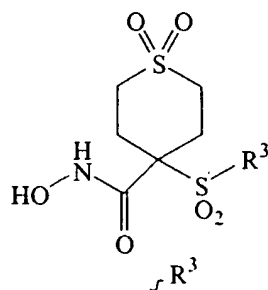
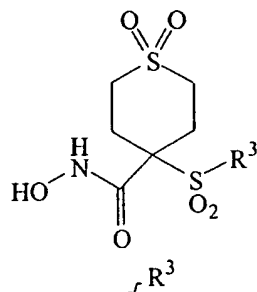


Table 88



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

Table 89

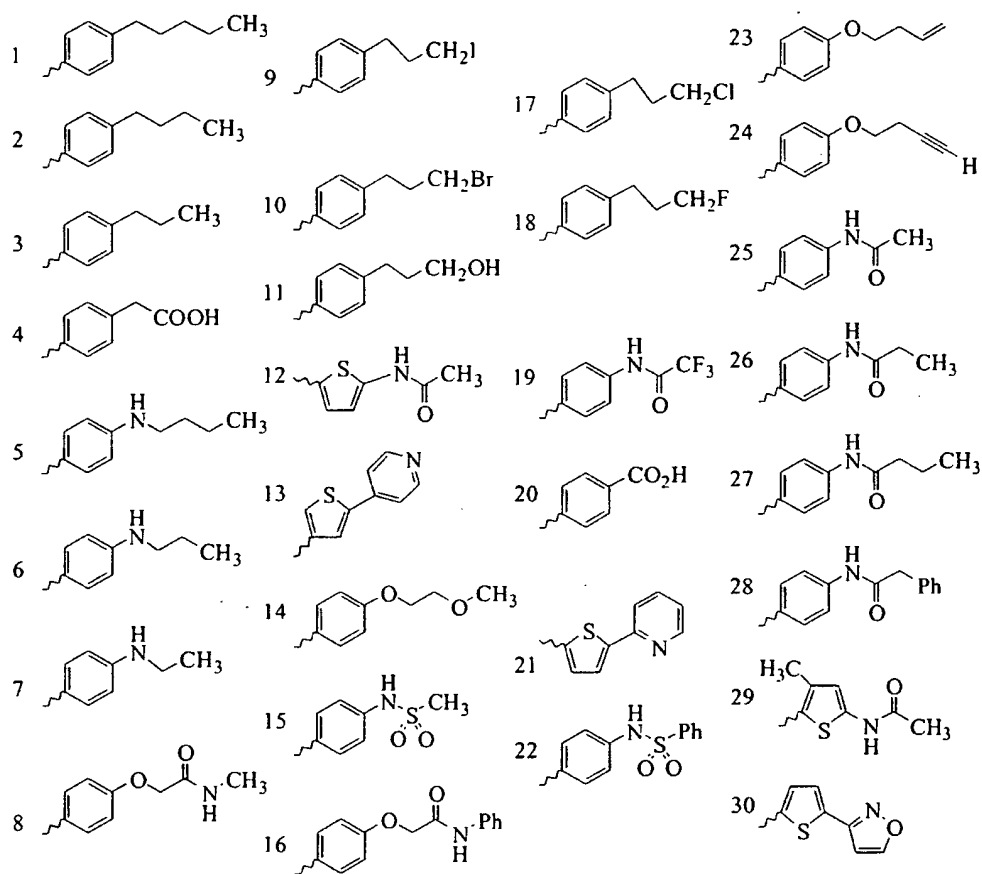
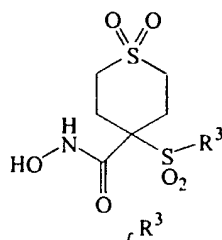


Table 90

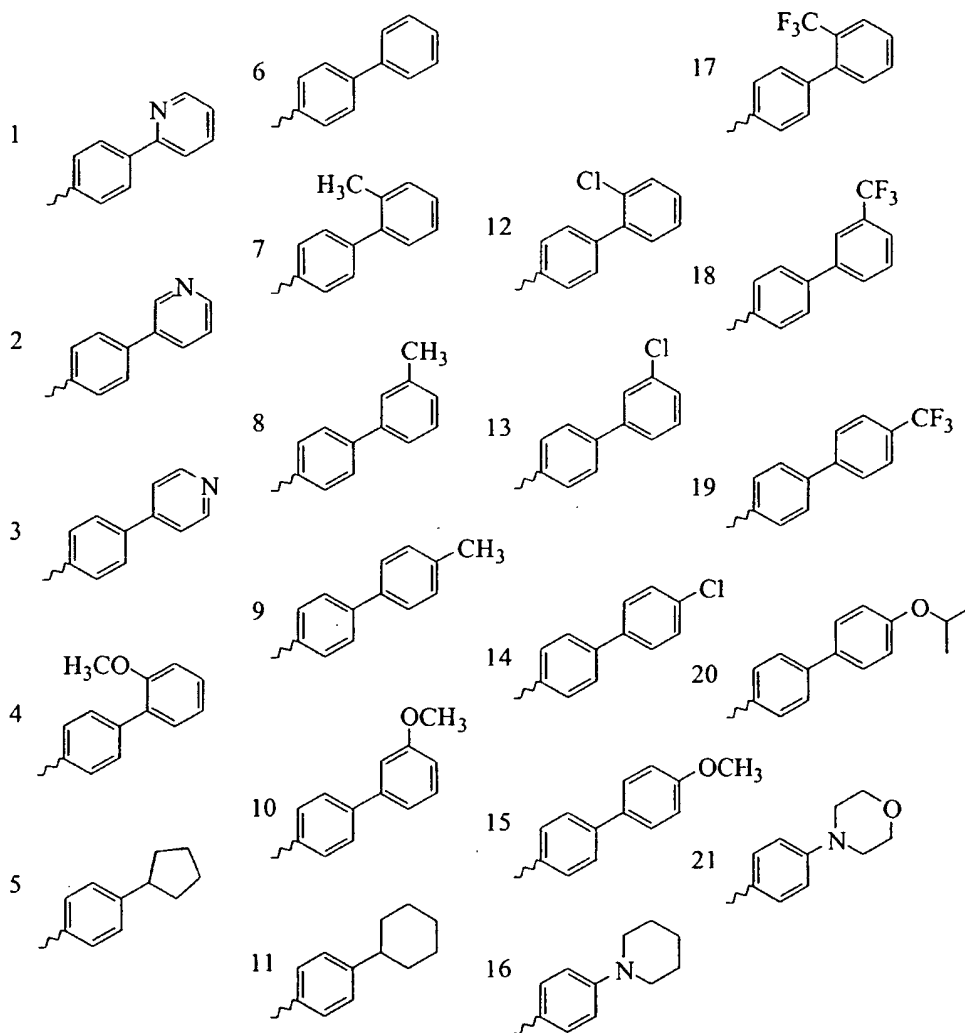
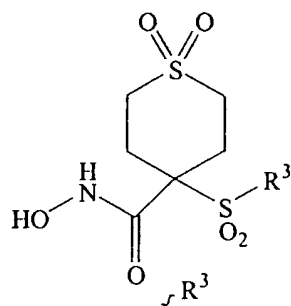


Table 91

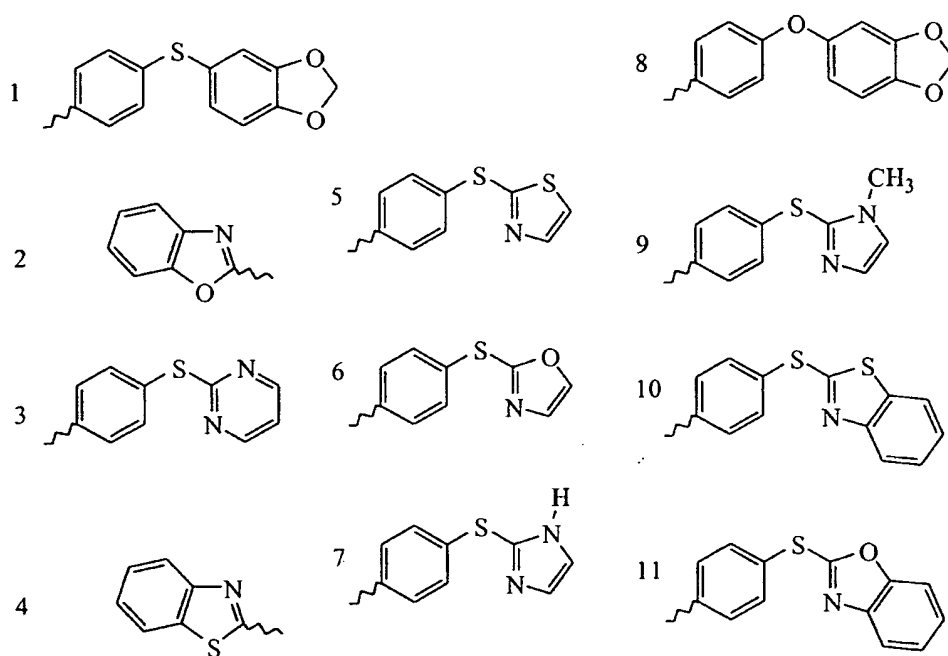
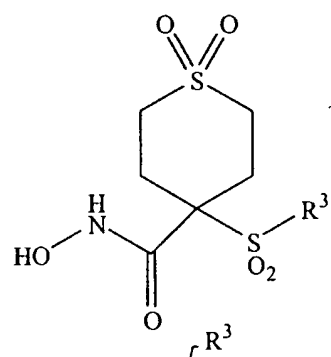
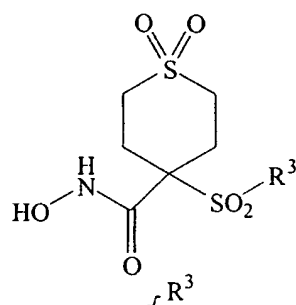


Table 92



1 	8 	15
2 	9 	16
3 	10 	17
4 	11 	18
5 	12 	19
6 	13 	20
7 	14 	21

Table 93

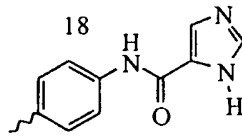
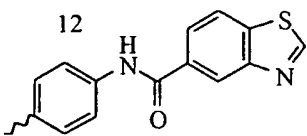
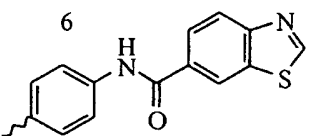
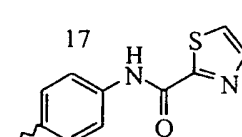
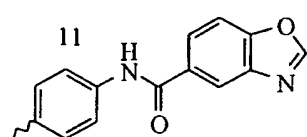
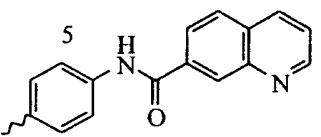
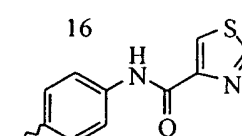
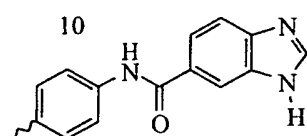
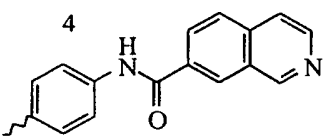
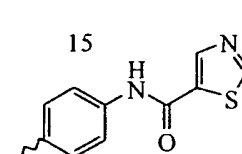
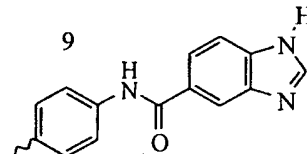
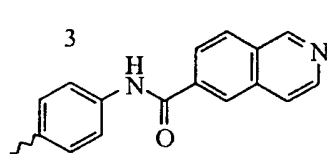
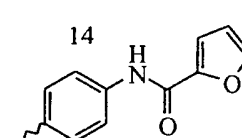
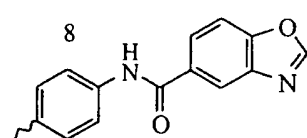
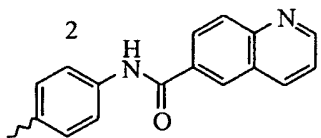
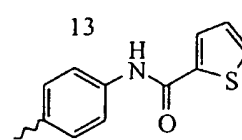
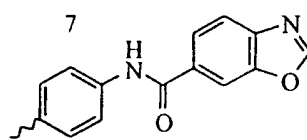
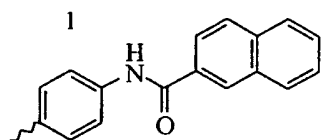
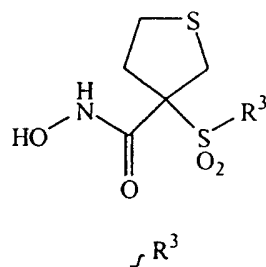


Table 94

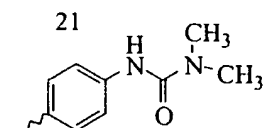
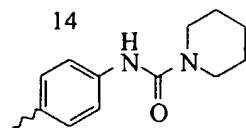
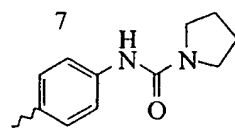
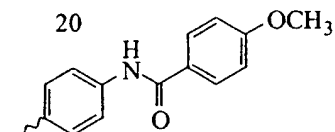
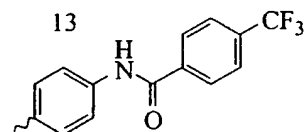
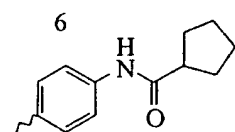
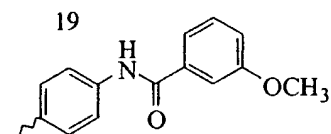
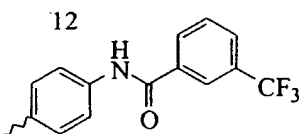
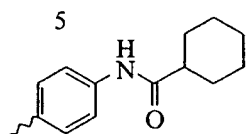
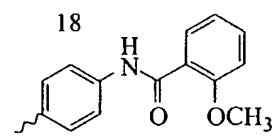
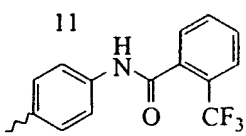
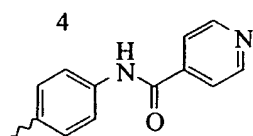
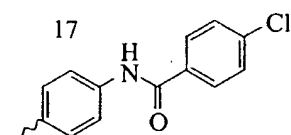
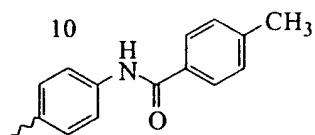
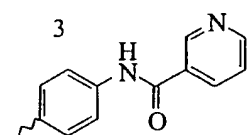
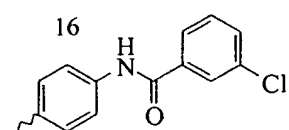
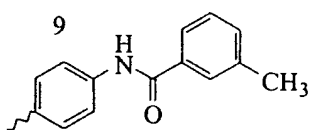
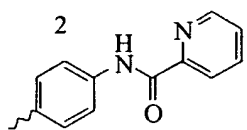
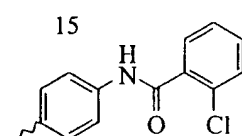
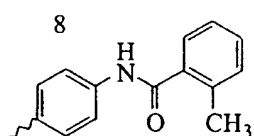
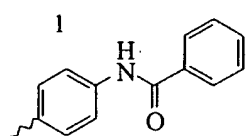
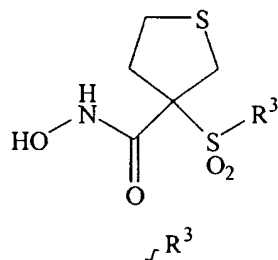
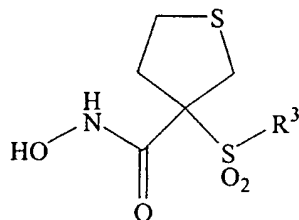


Table 95



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

Table 97

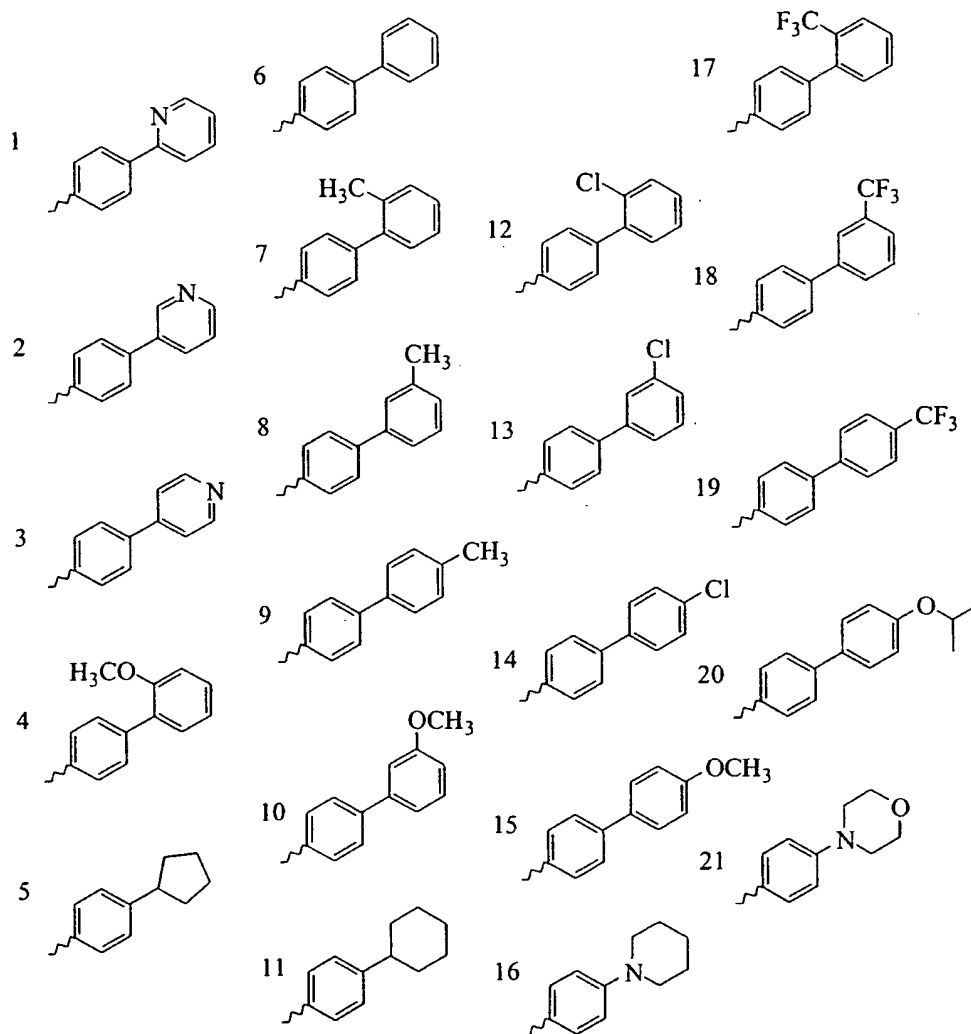
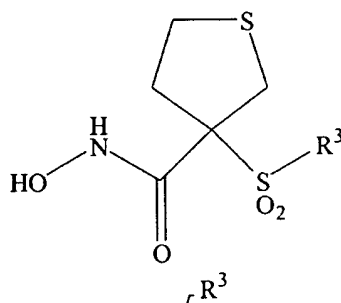


Table 98

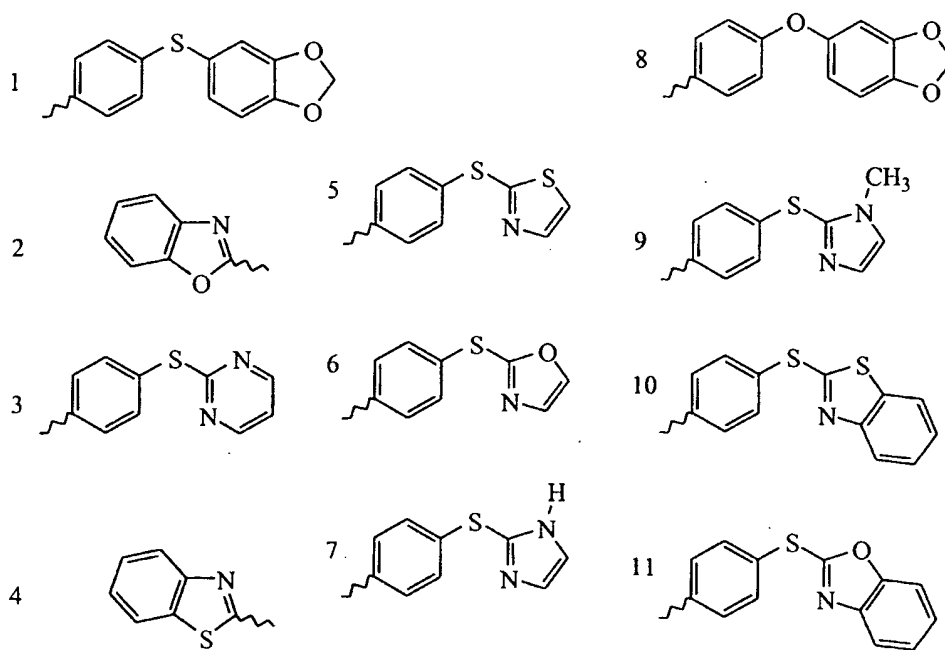
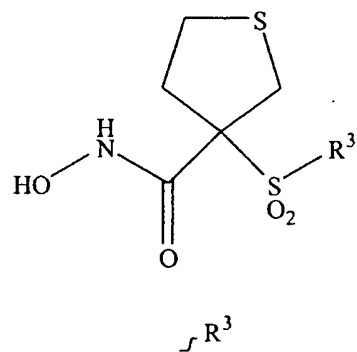
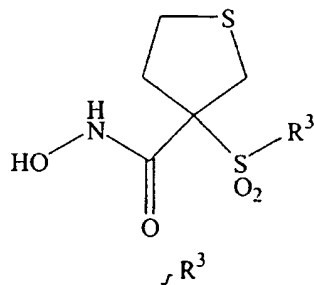


Table 99



1	8	15
2	9	16
3	10	17
4	11	18
5	12	19
6	13	20
7	14	21

Table 100

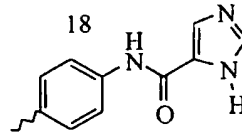
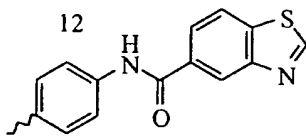
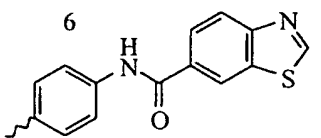
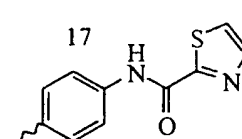
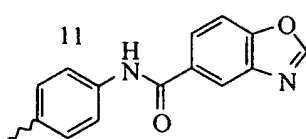
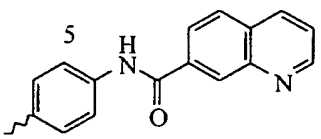
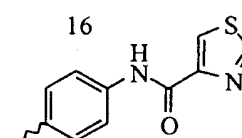
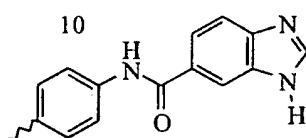
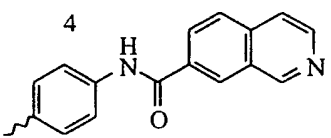
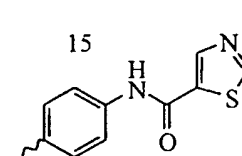
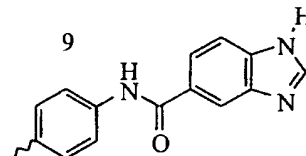
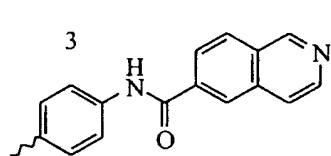
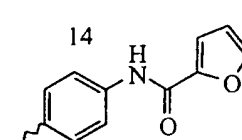
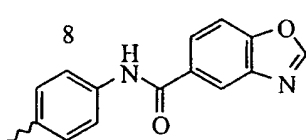
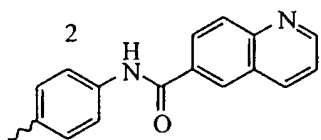
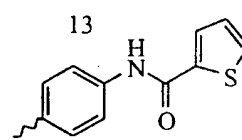
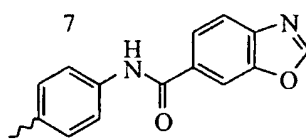
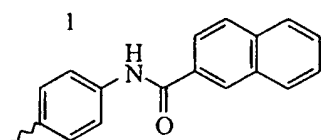
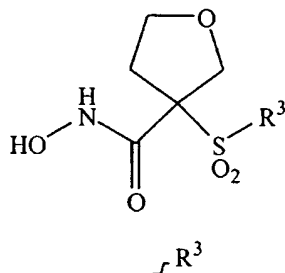


Table 101

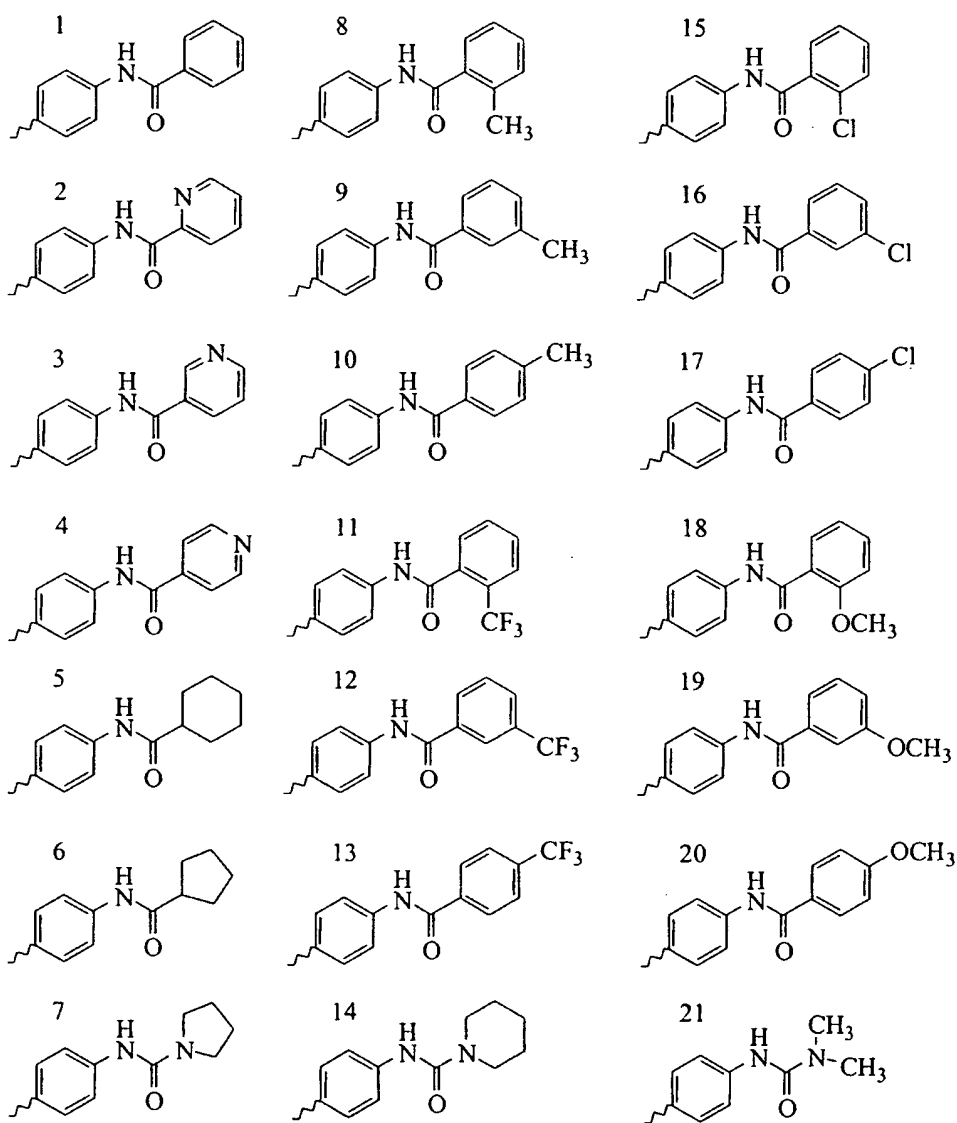
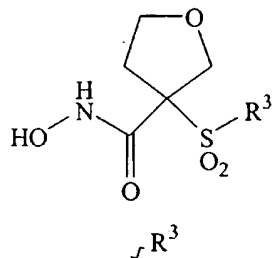
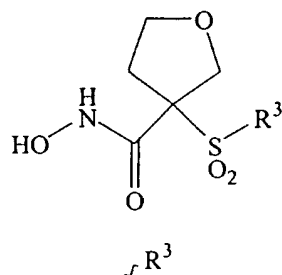


Table 102



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

Table 103

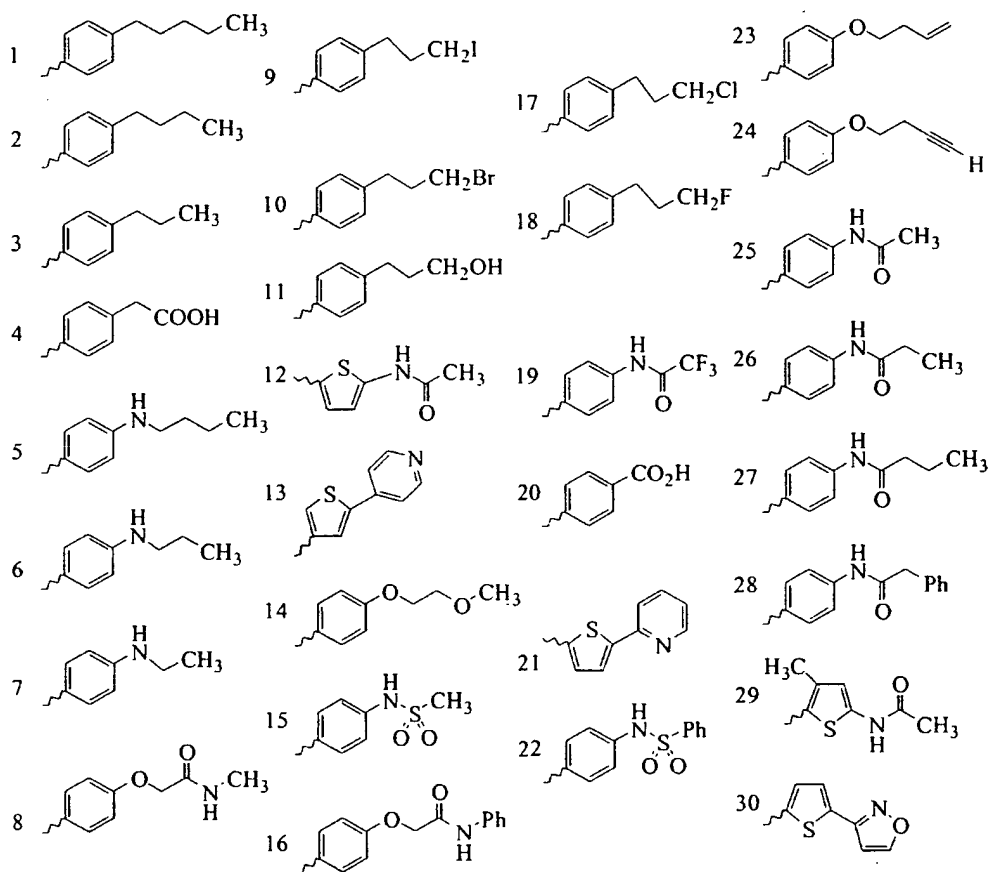
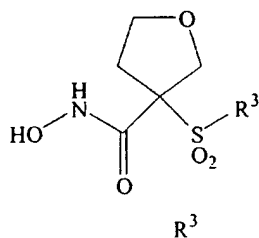


Table 104

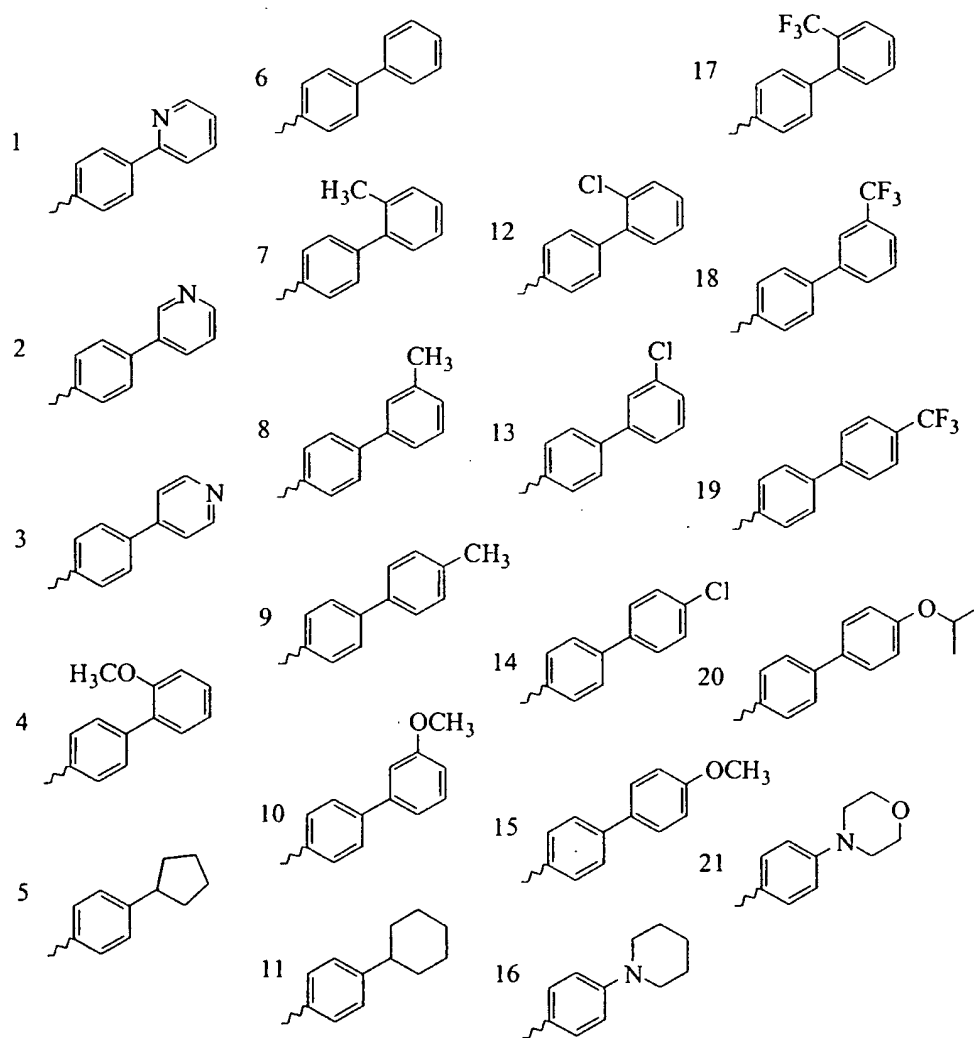
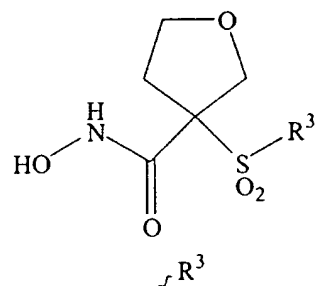
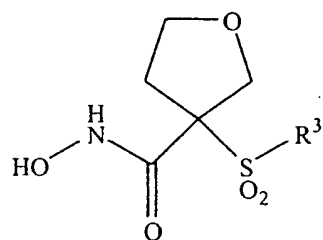


Table 105



R^3

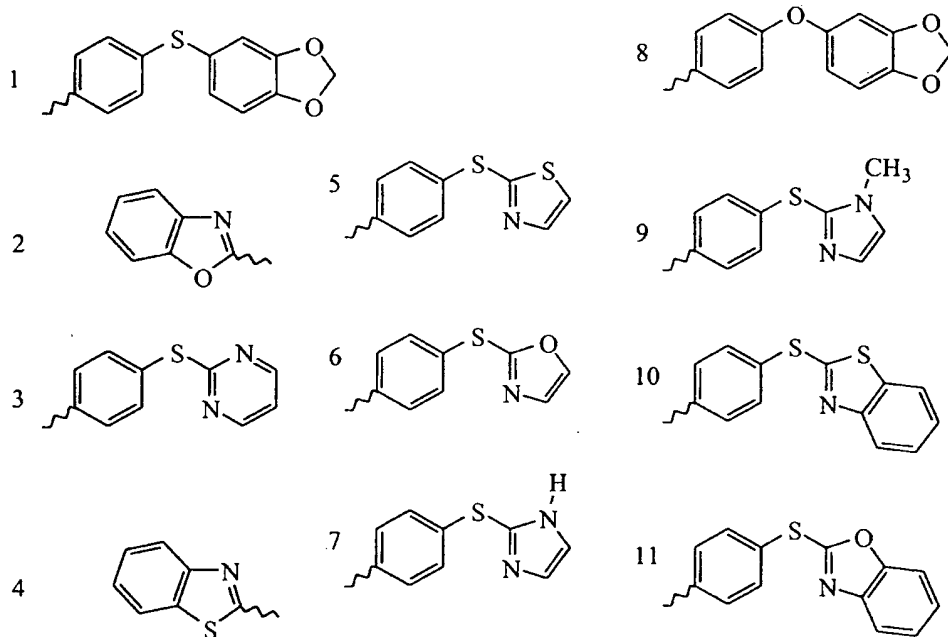


Table 106

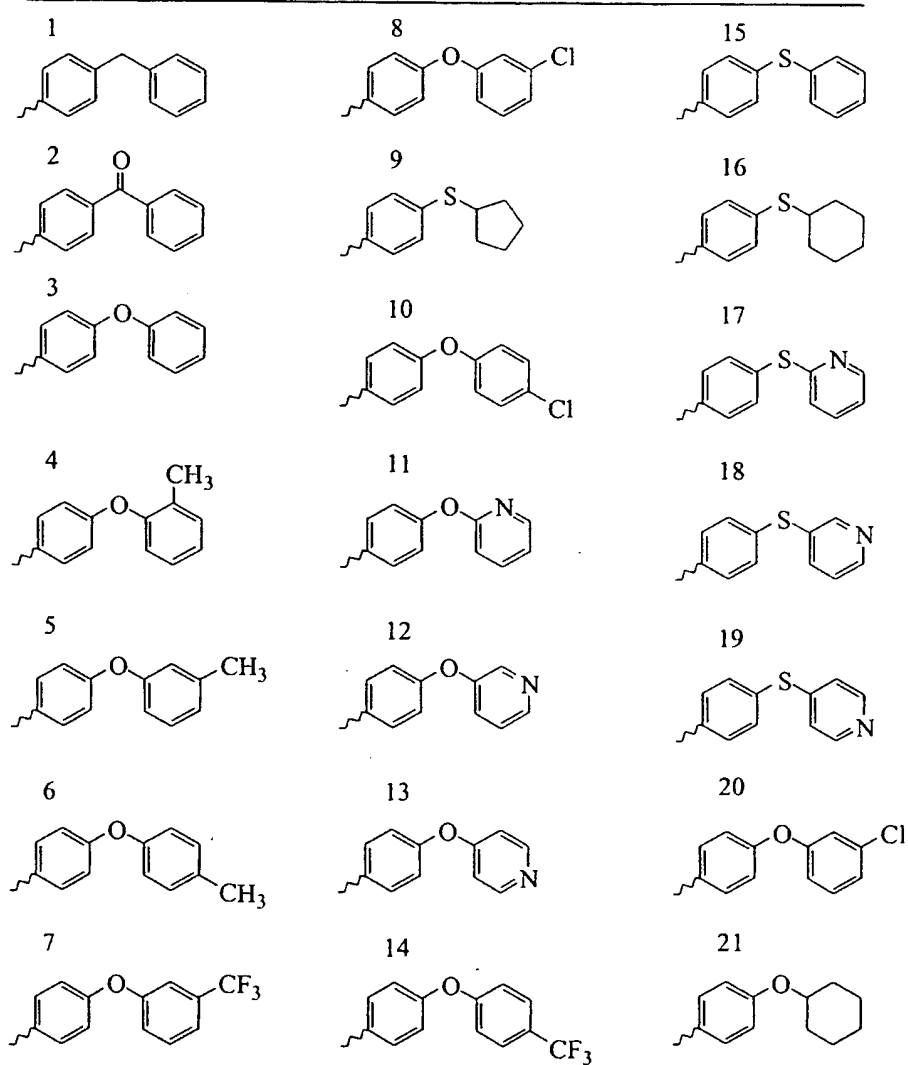
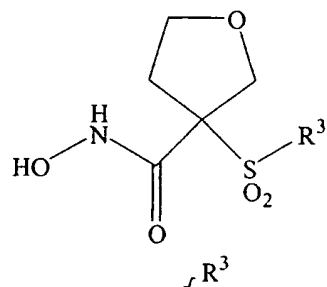


Table 107

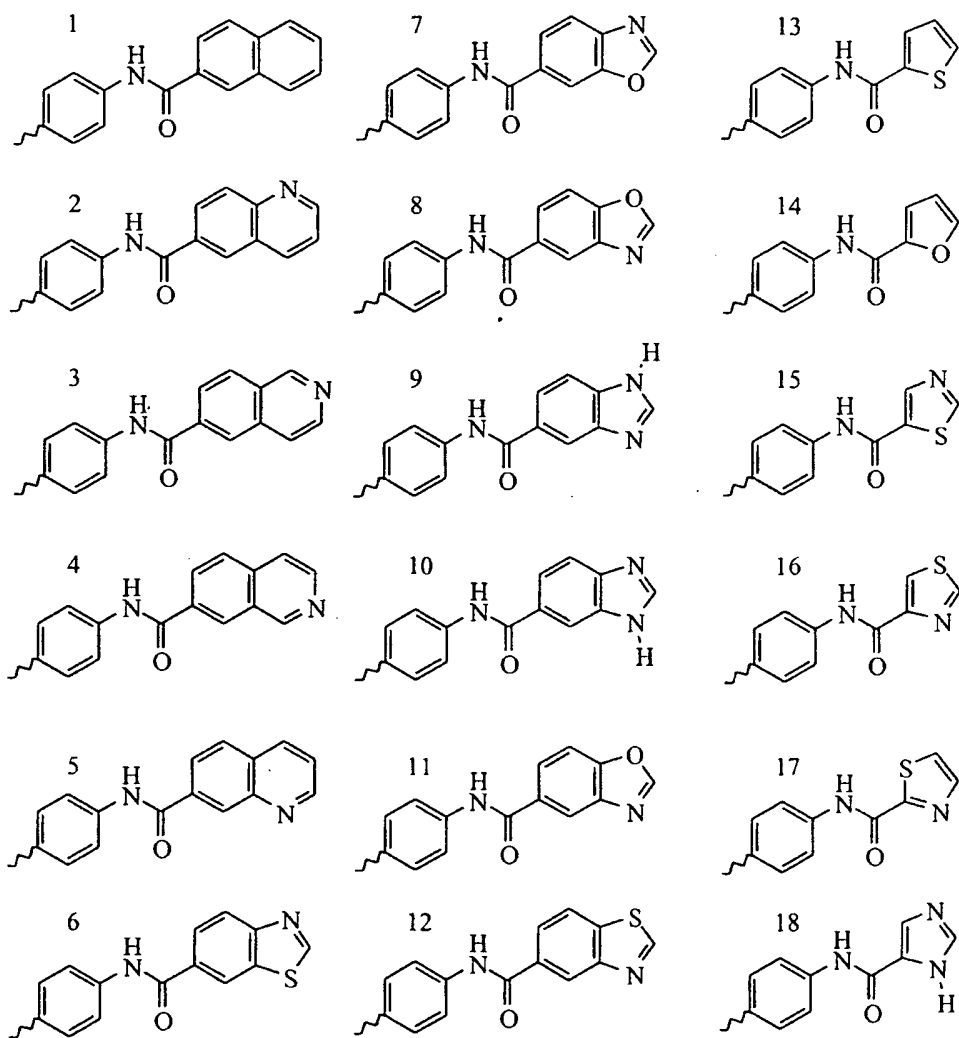
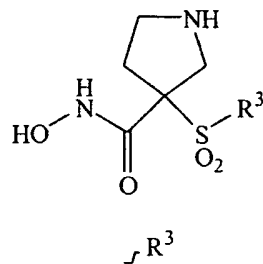


Table 108

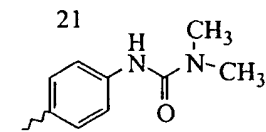
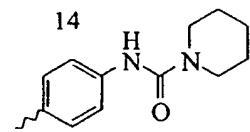
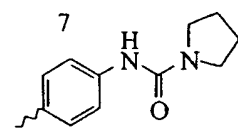
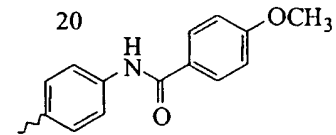
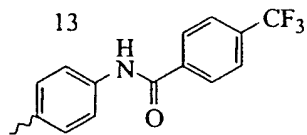
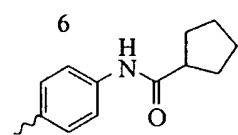
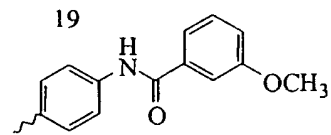
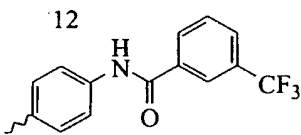
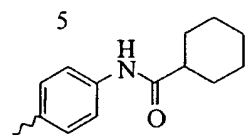
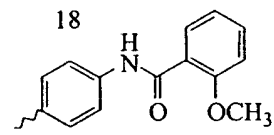
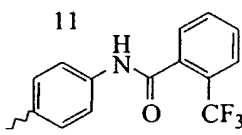
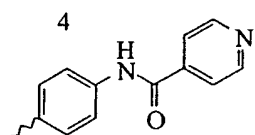
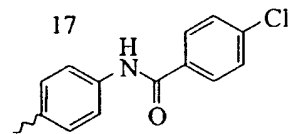
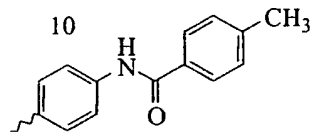
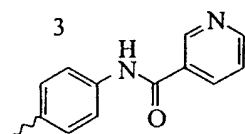
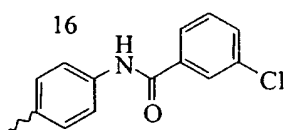
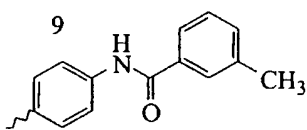
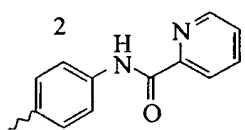
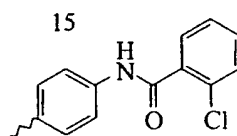
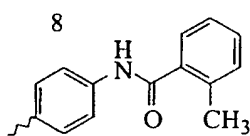
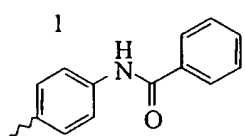
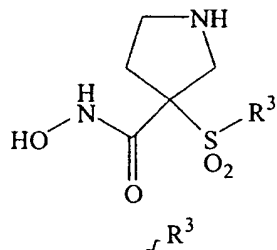
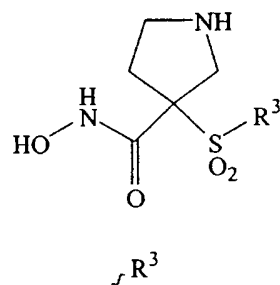


Table 109



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

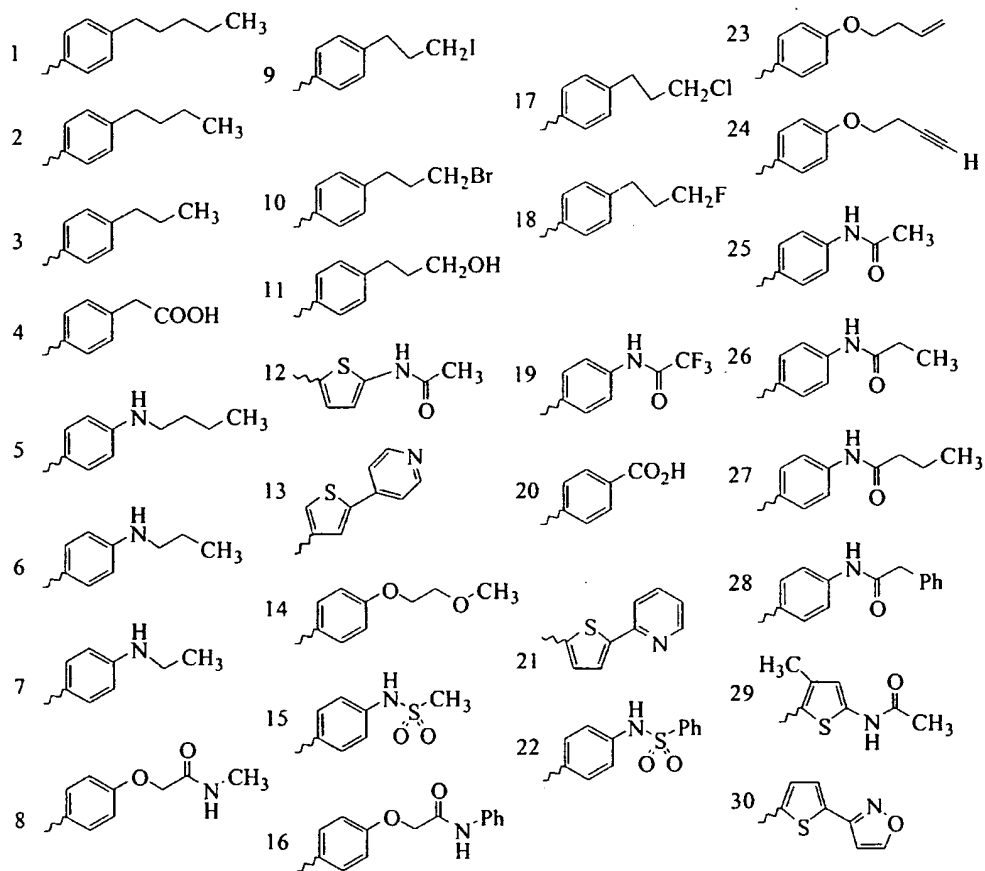
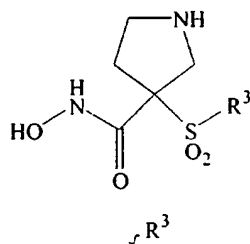
Table 110

Table 111

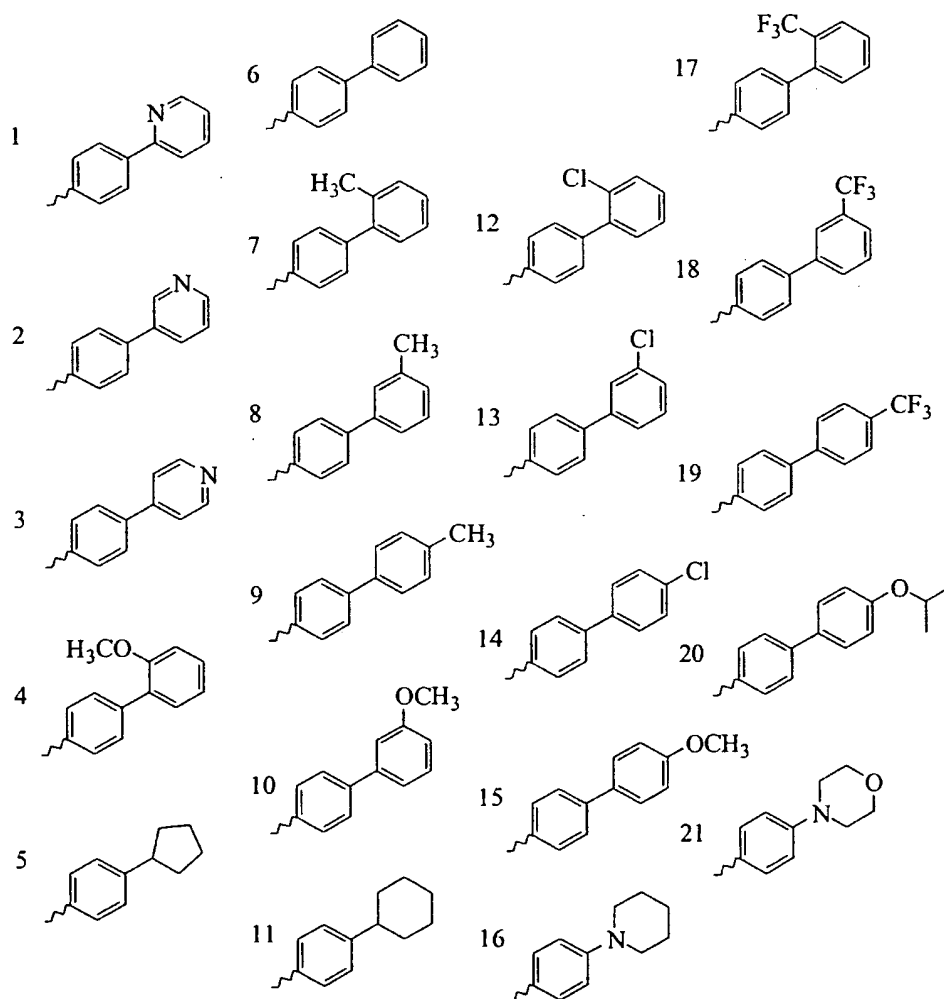
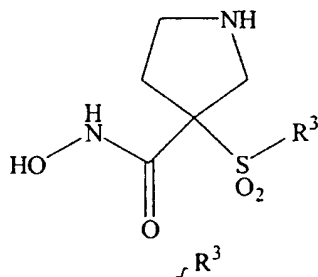


Table 112

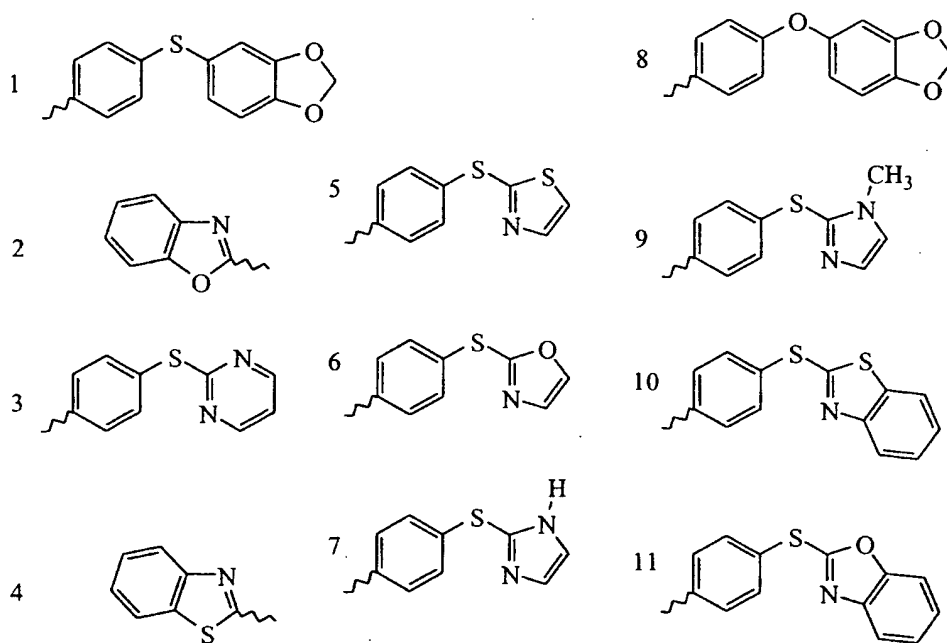
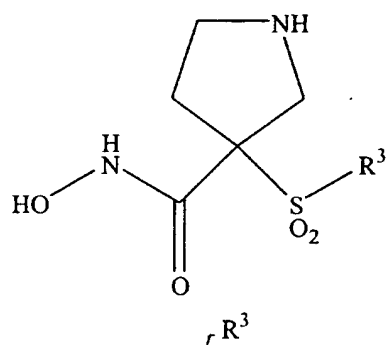
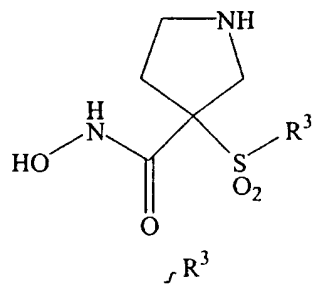


Table 113



1 	8 	15
2 	9 	16
3 	10 	17
4 	11 	18
5 	12 	19
6 	13 	20
7 	14 	21

Table 114

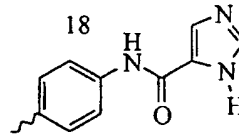
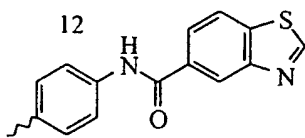
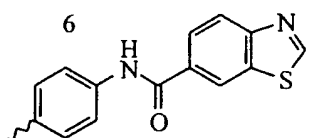
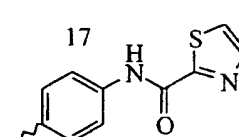
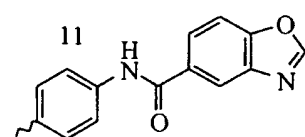
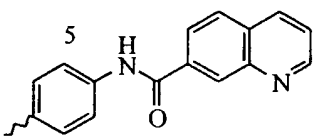
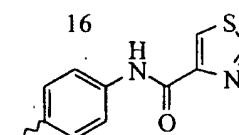
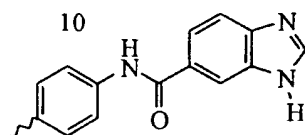
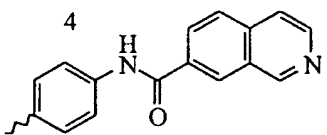
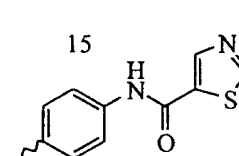
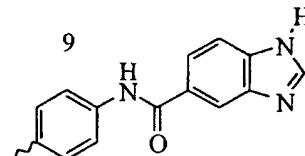
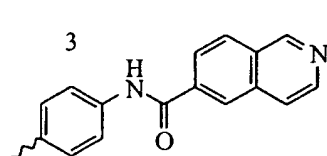
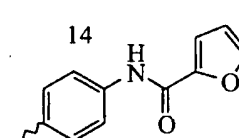
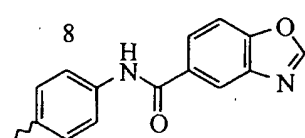
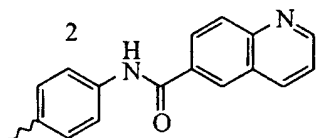
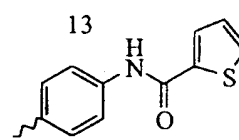
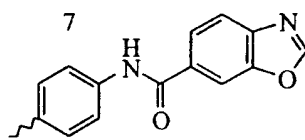
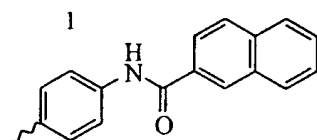
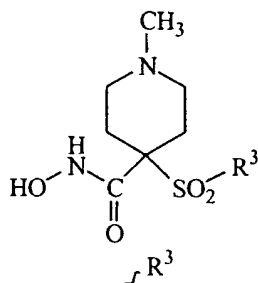


Table 115

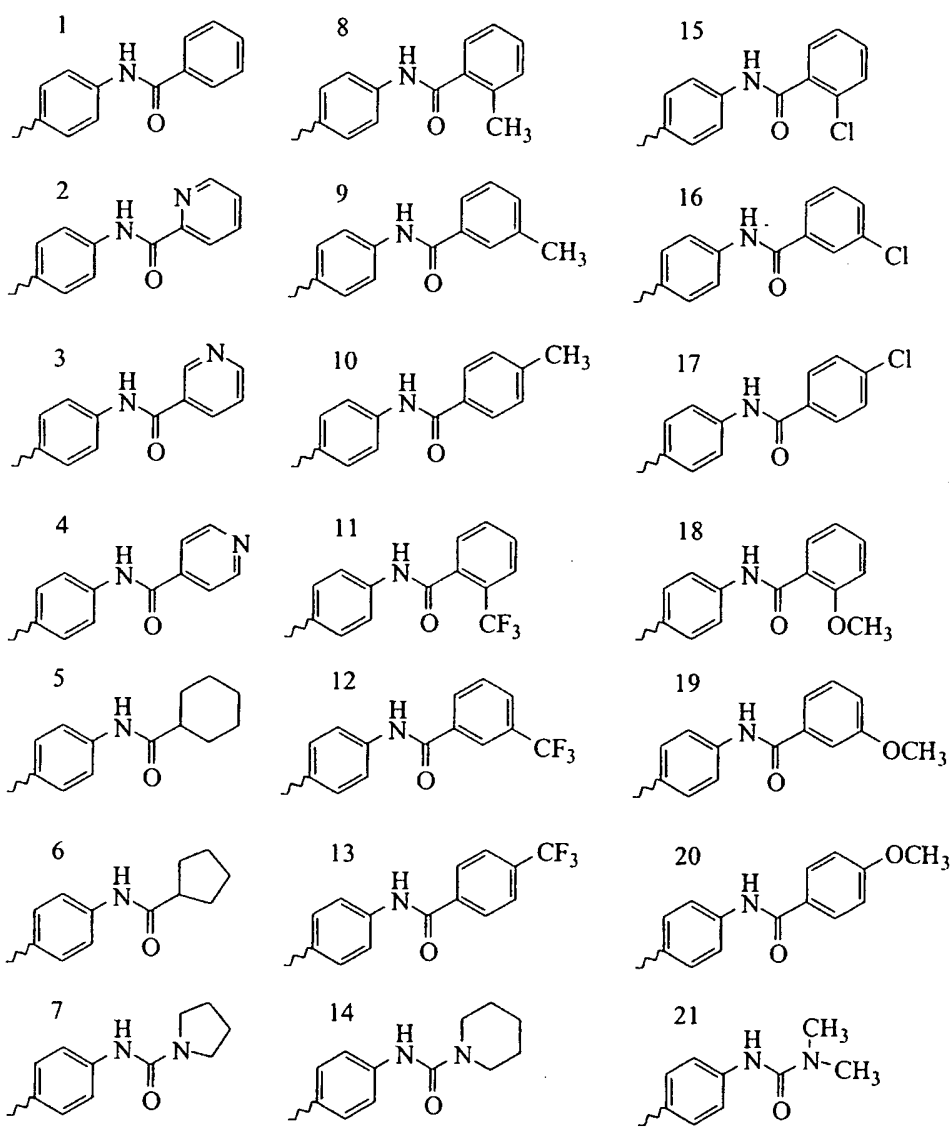
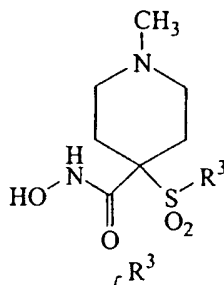
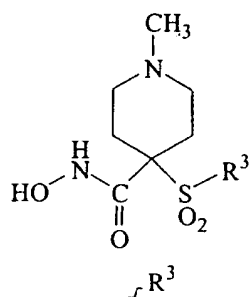


Table 116



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

Table 117

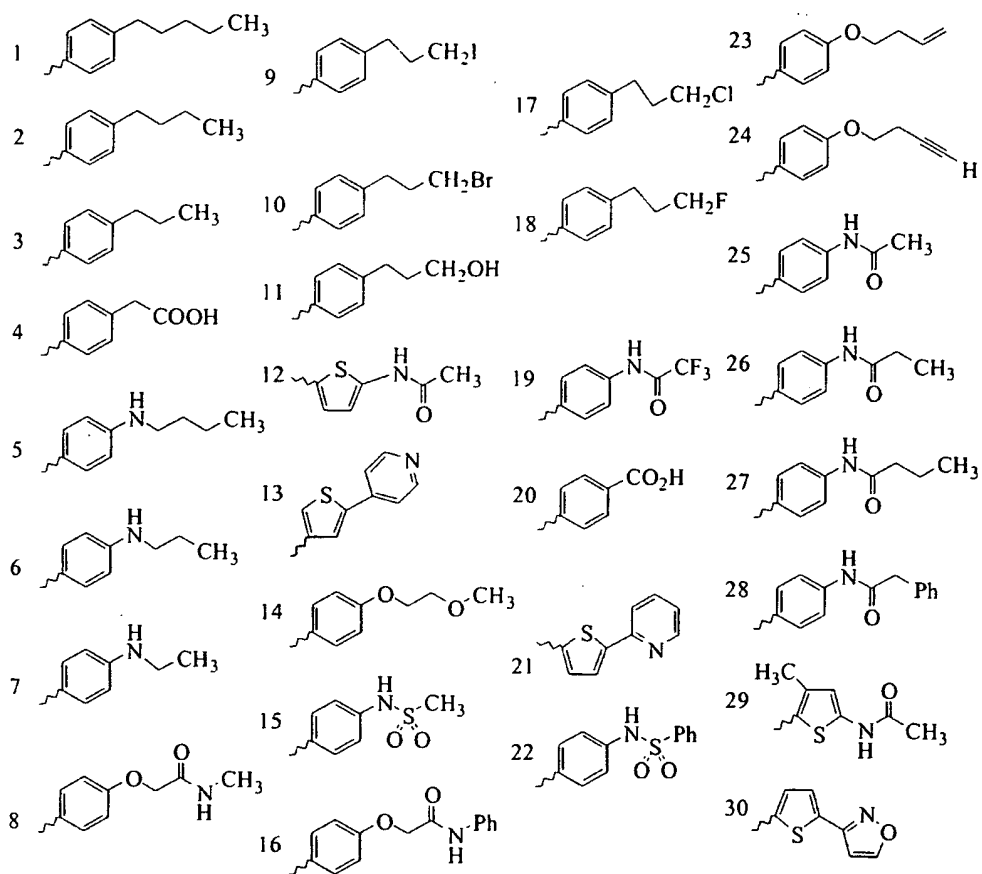
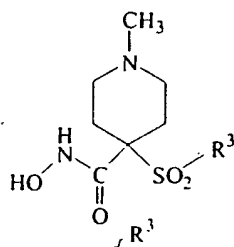


Table 118

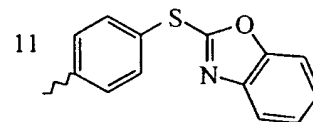
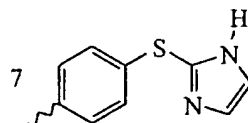
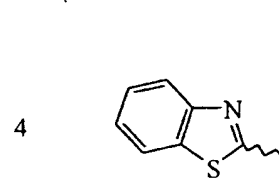
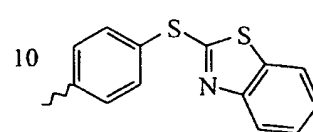
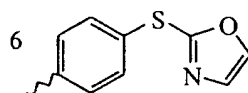
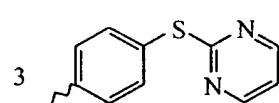
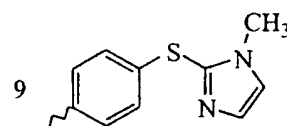
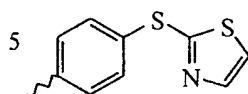
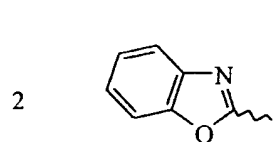
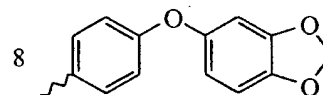
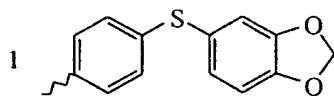
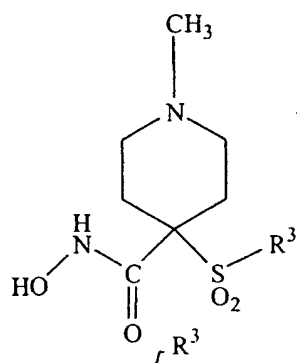
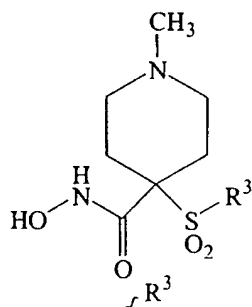


Table 119



1 	8 	15
2 	9 	16
3 	10 	17
4 	11 	18
5 	12 	19
6 	13 	20
7 	14 	21

Table 120

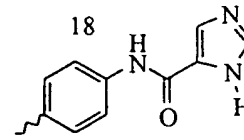
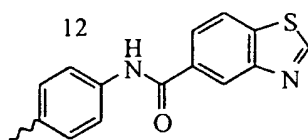
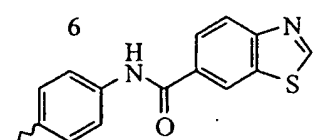
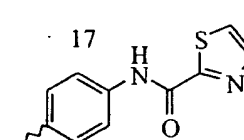
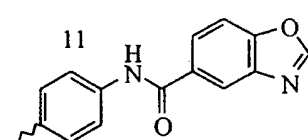
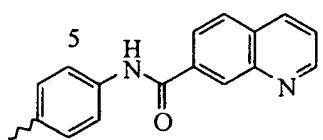
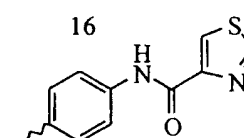
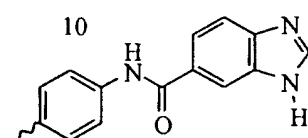
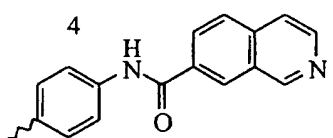
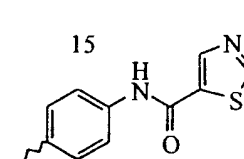
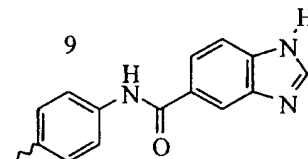
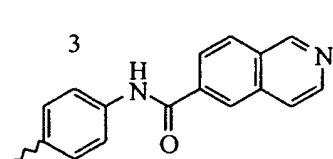
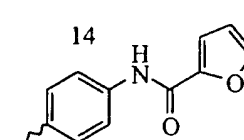
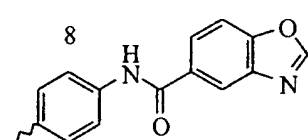
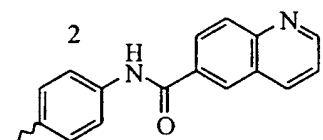
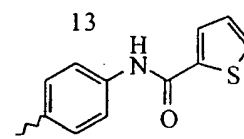
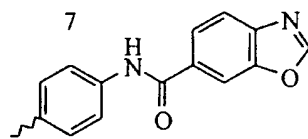
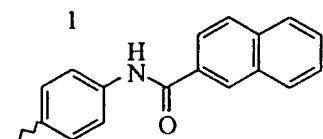
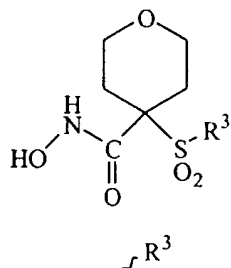


Table 121

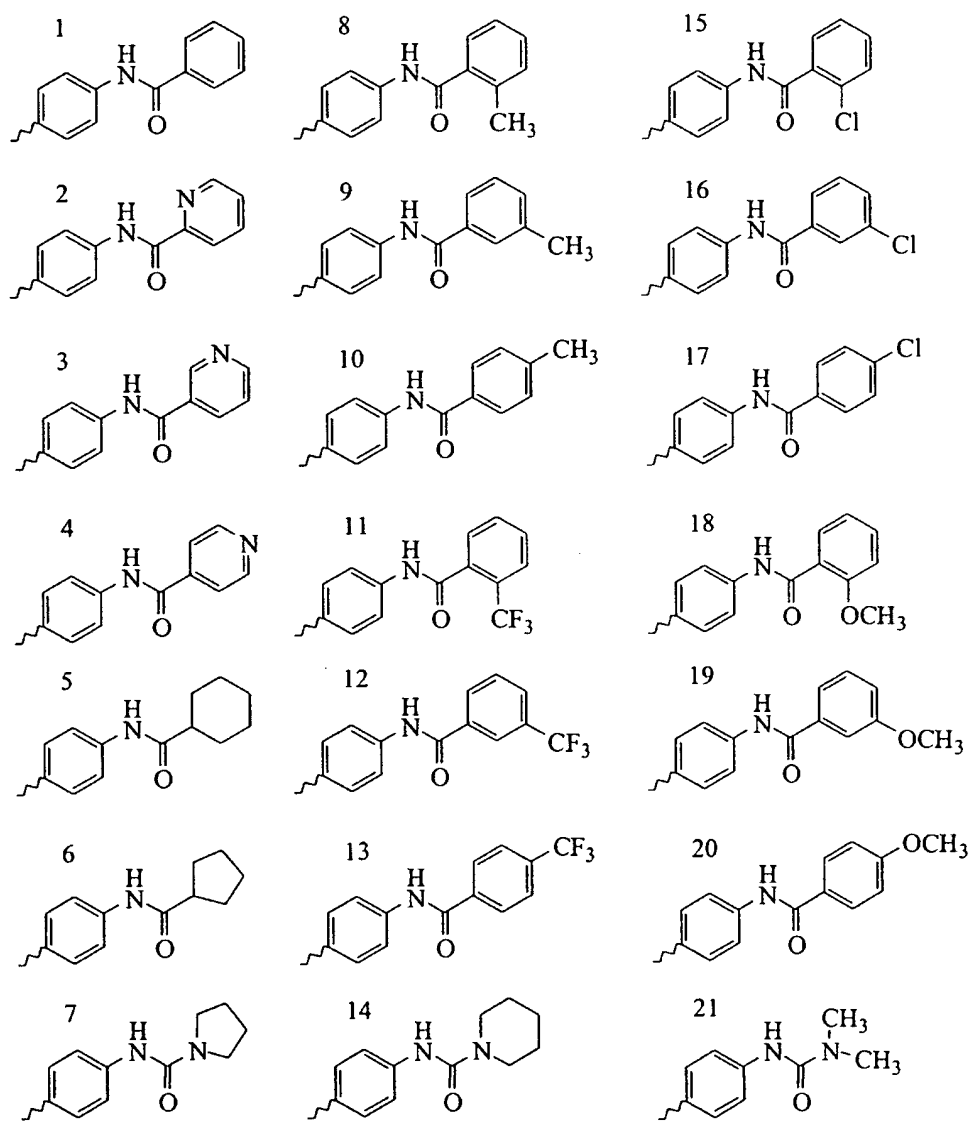
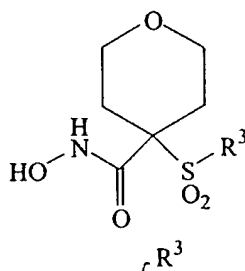
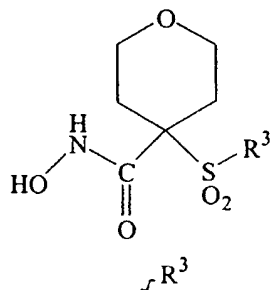


Table 122



1 	9 	16
2 	10 	17
3 	11 	18
4 	12 	19
5 	13 	20
6 	14 	21
7 	15 	22
8 		

Table 123

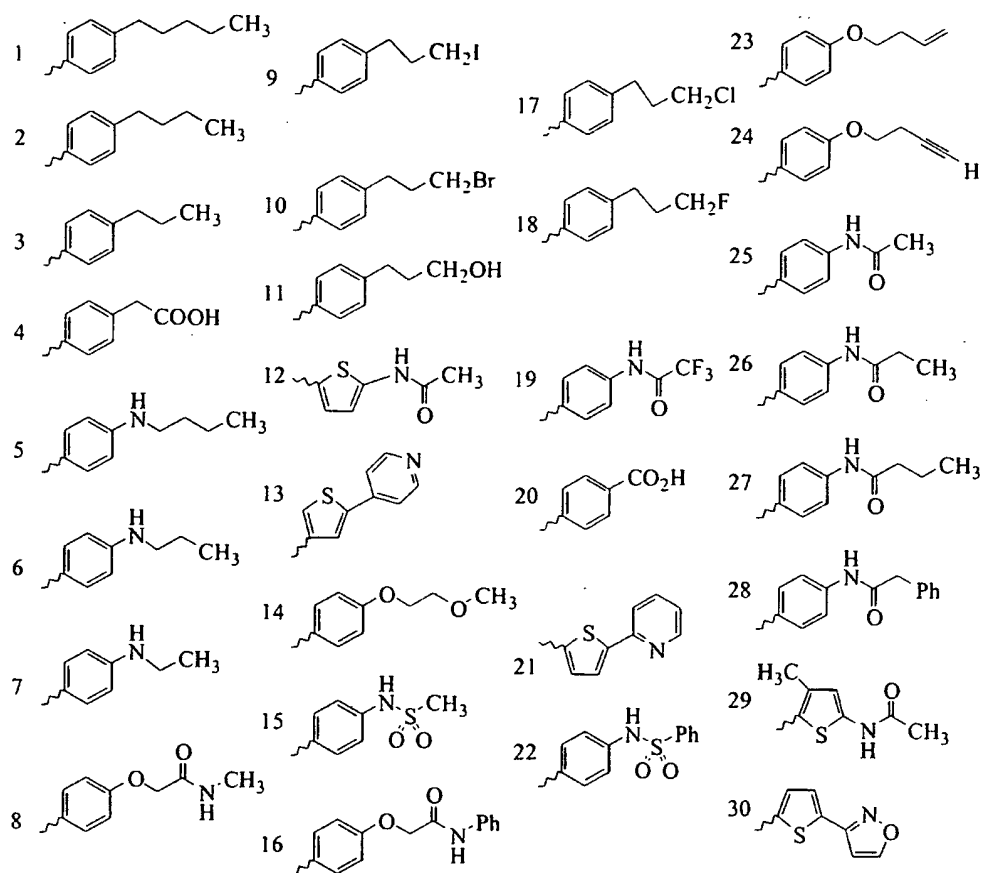
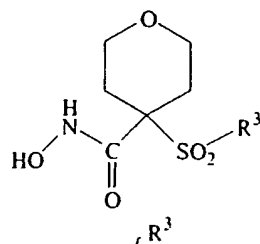


Table 124

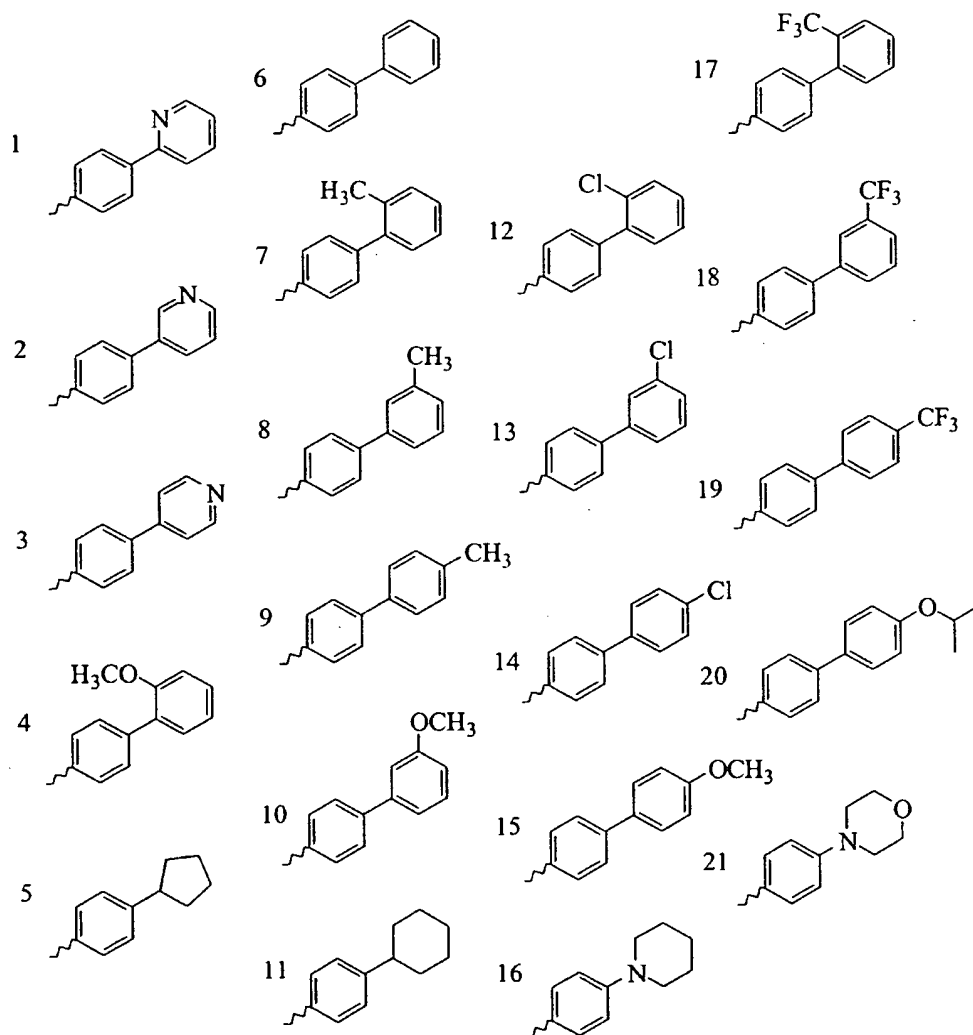
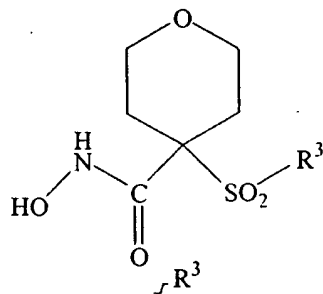


Table 125

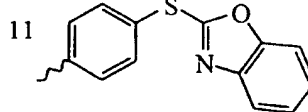
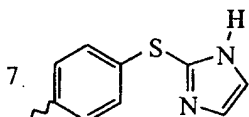
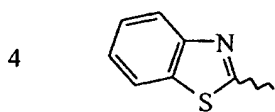
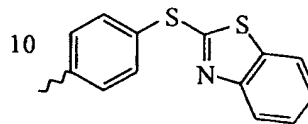
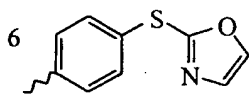
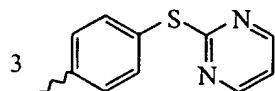
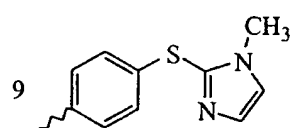
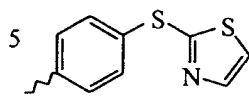
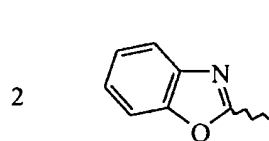
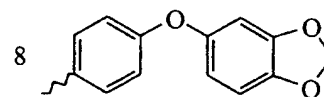
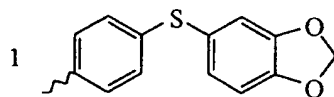
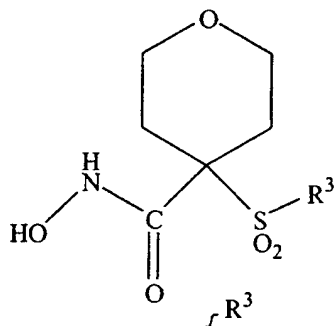


Table 126

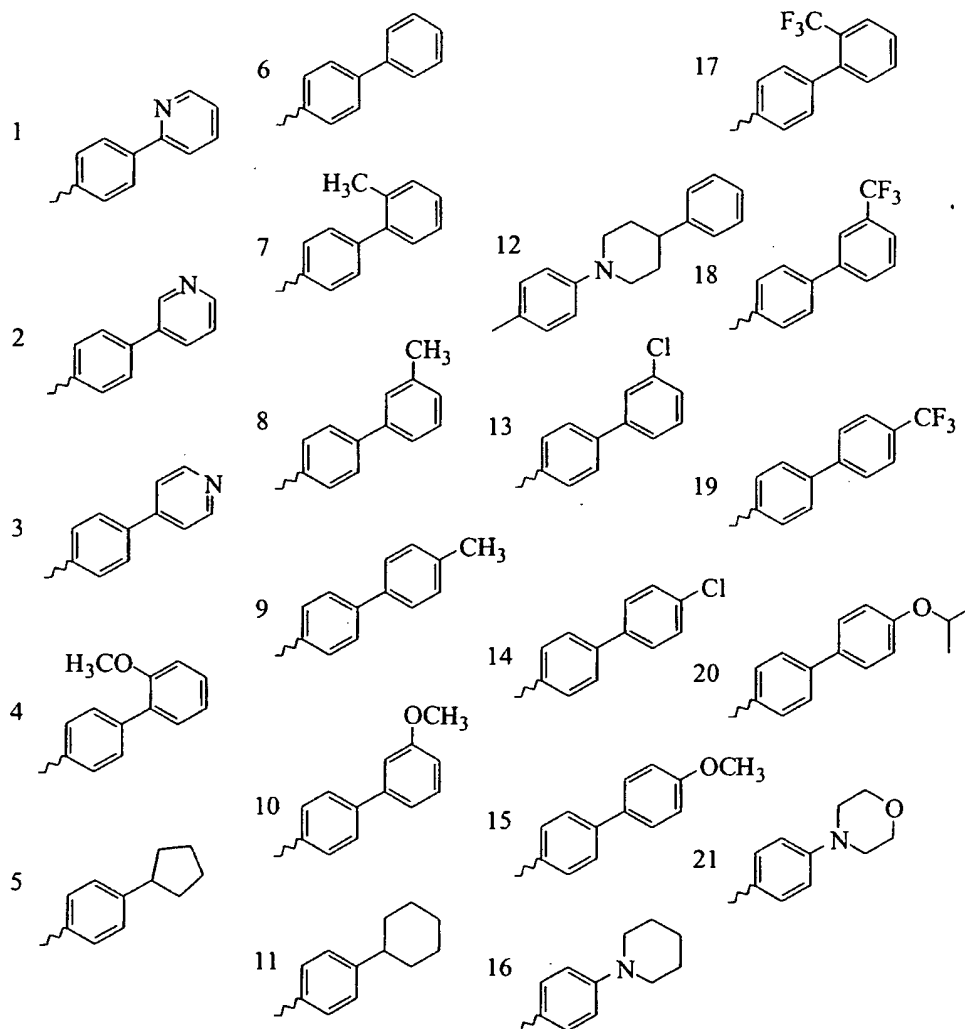
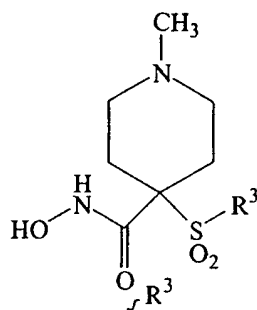
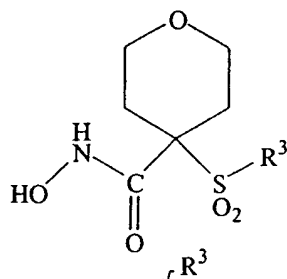


Table 127



1	8	15
2	9	16
3	10	17
4	11	18
5	12	19
6	13	20
7	14	21

Table 128

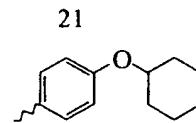
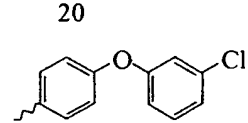
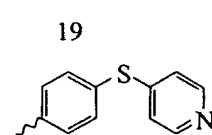
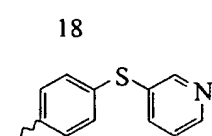
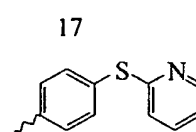
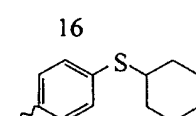
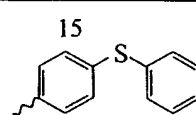
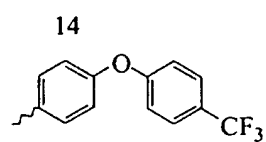
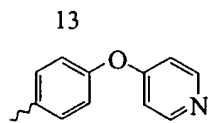
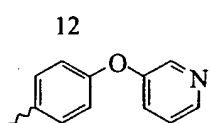
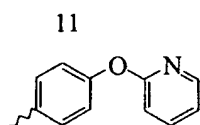
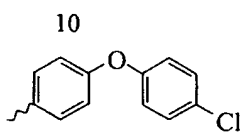
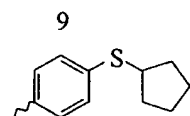
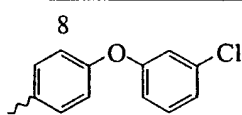
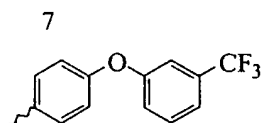
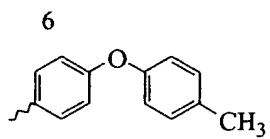
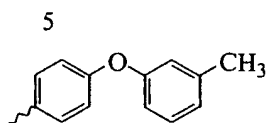
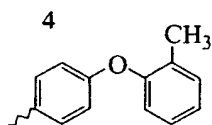
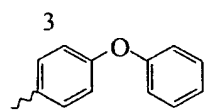
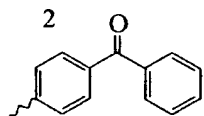
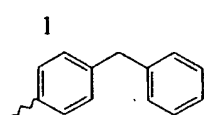
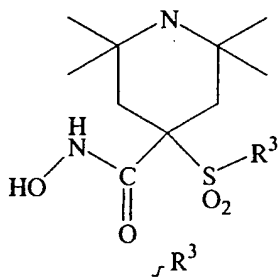


Table 129

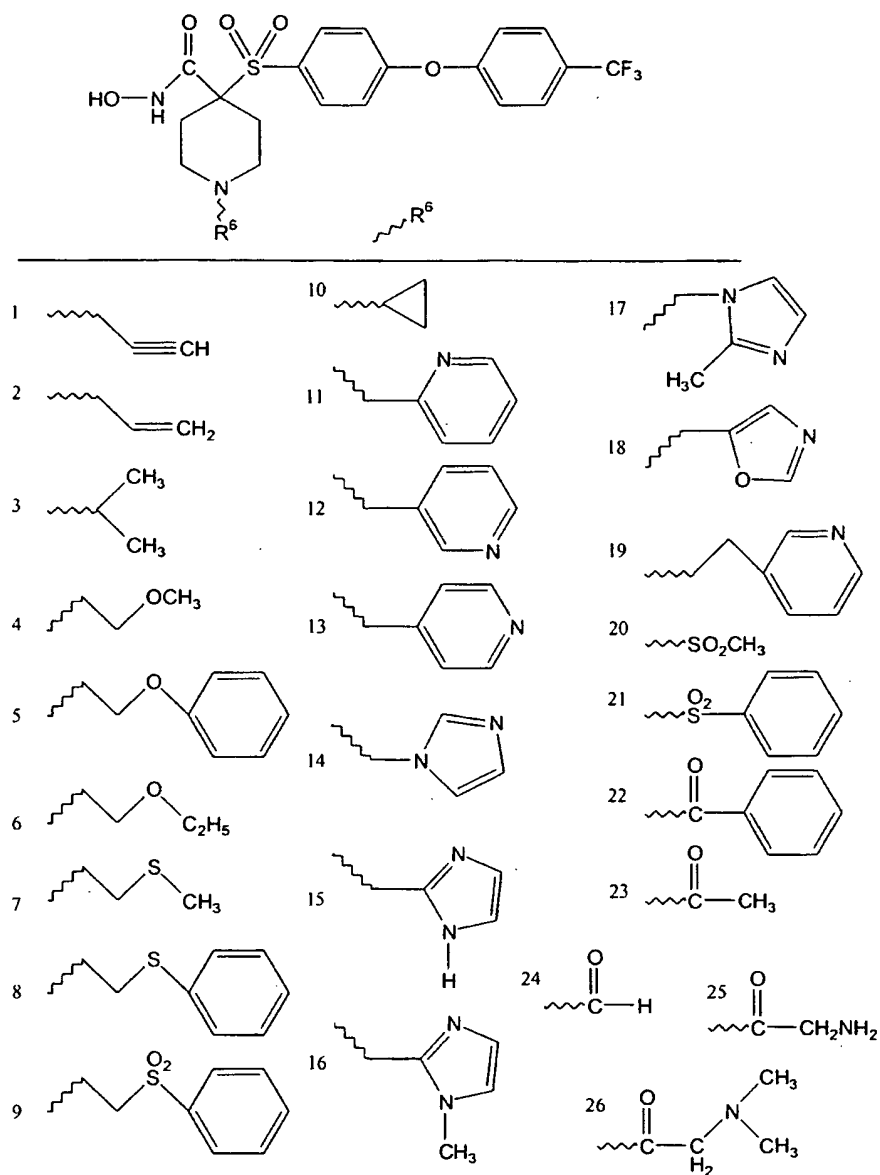


Table 130

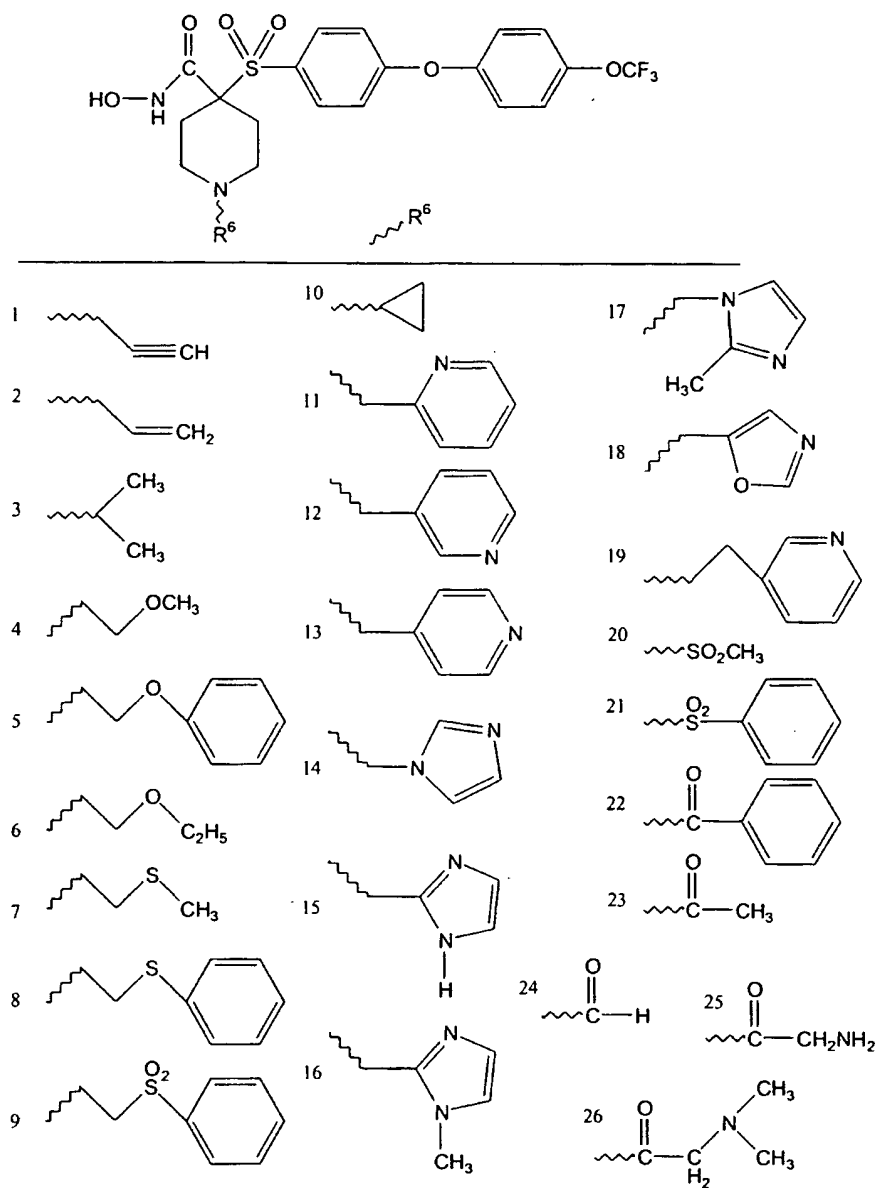


Table 131

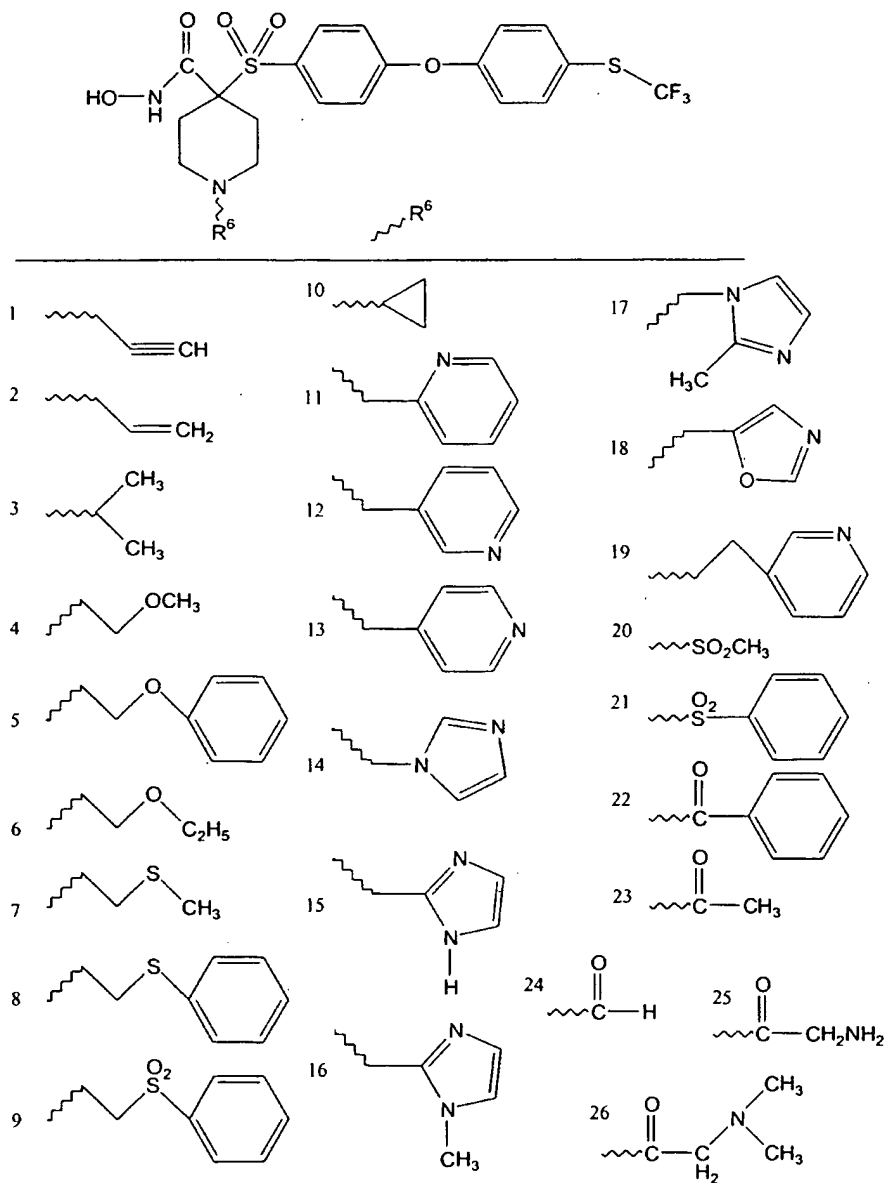


Table 132

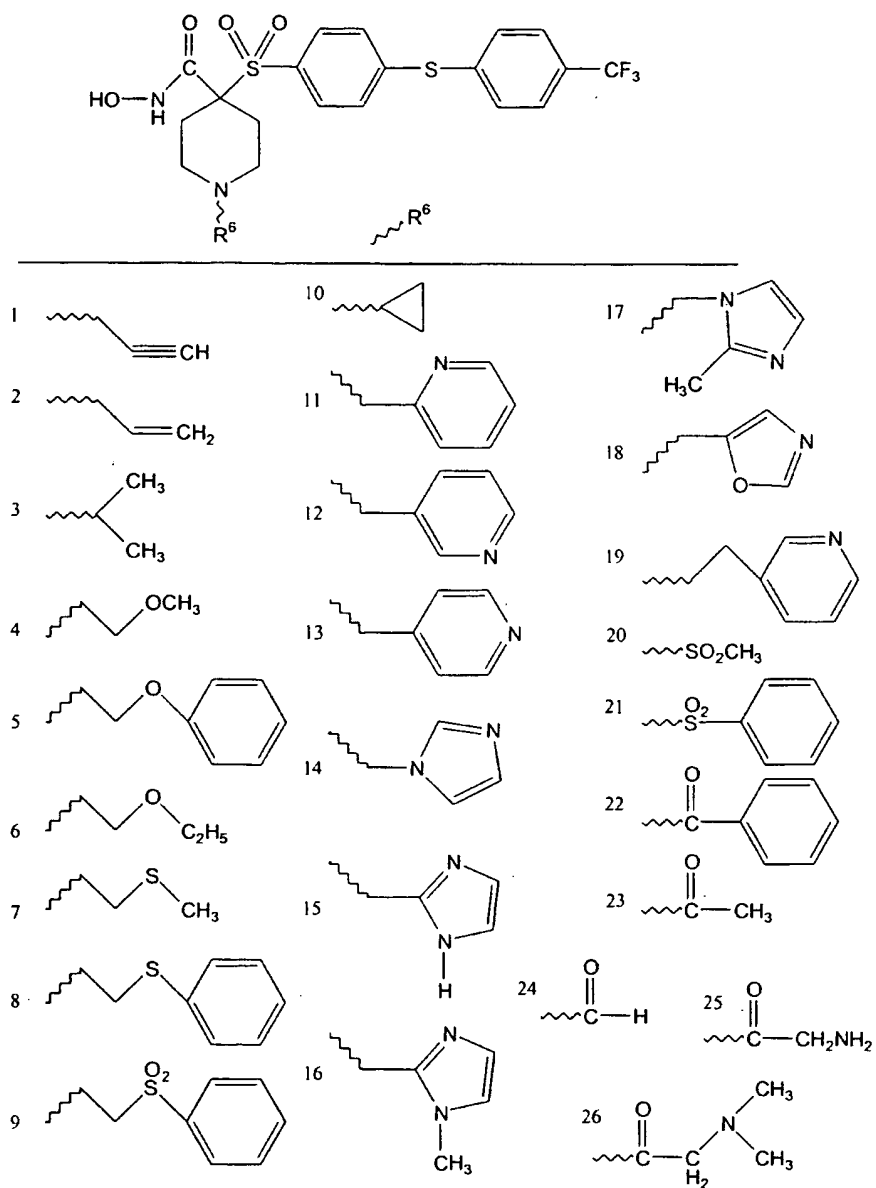


Table 133

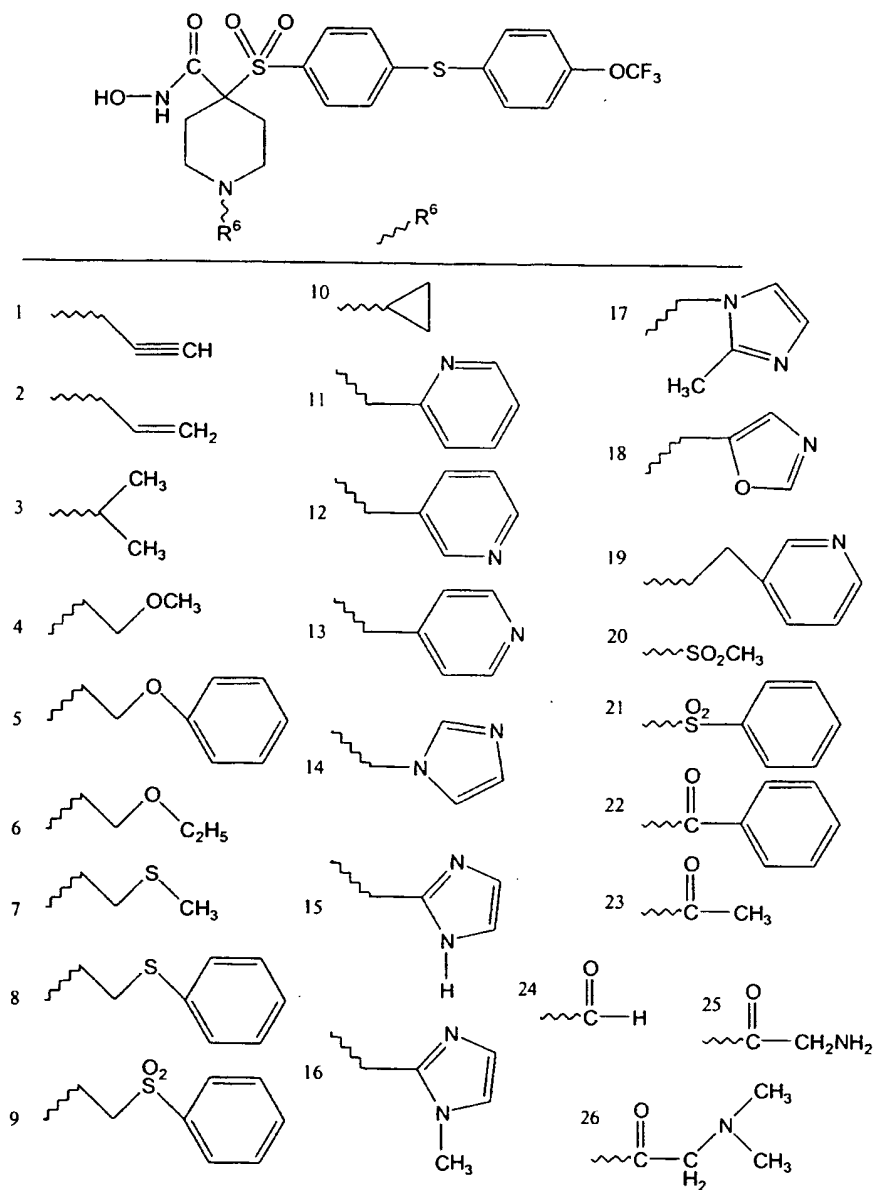


Table 134

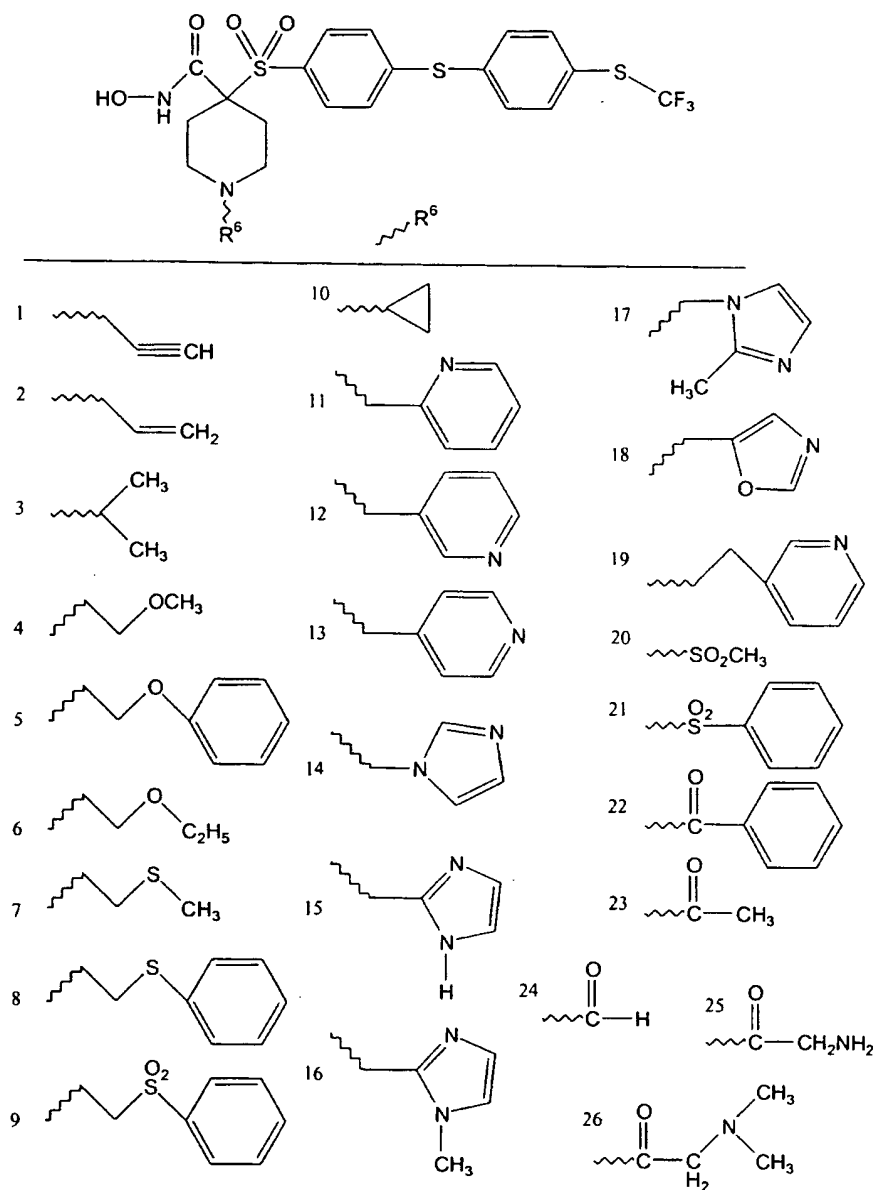


Table 135

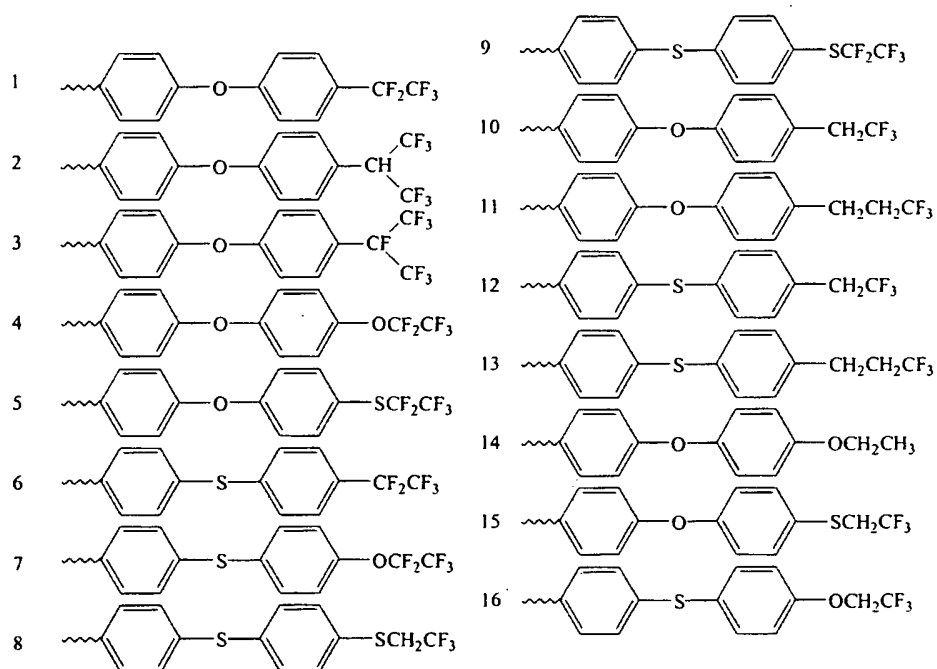
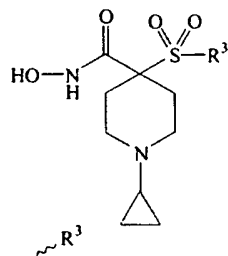
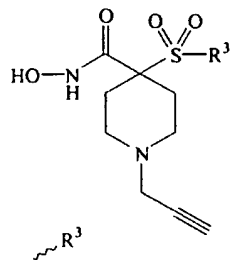
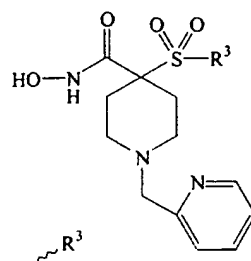


Table 136



1		9	
2		10	
3		11	
4		12	
5		13	
6		14	
7		15	
8		16	

Table 137



1		9	
2		10	
3		11	
4		12	
5		13	
6		14	
7		15	
8		16	

Table 138

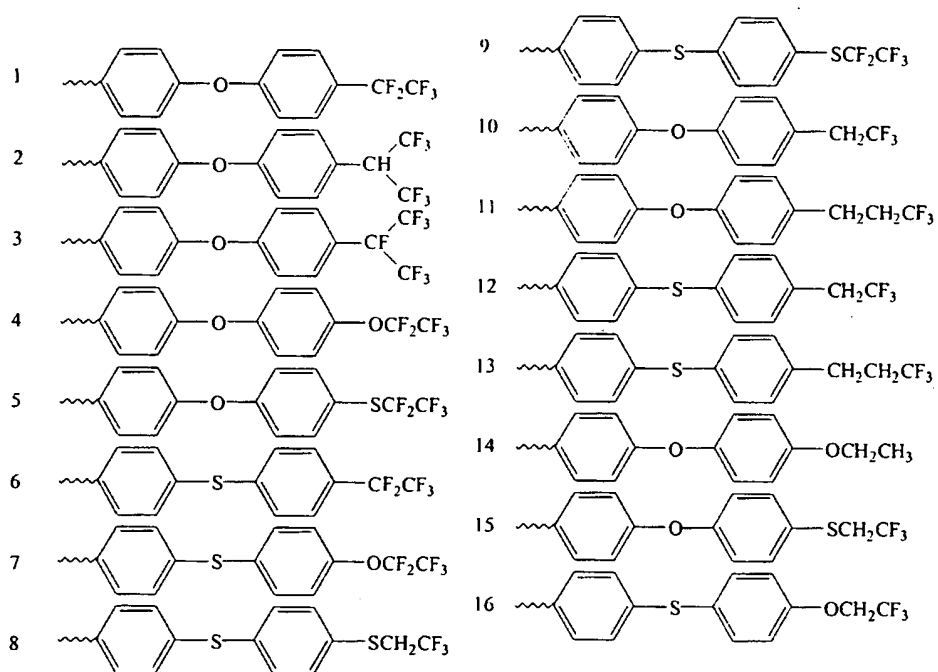
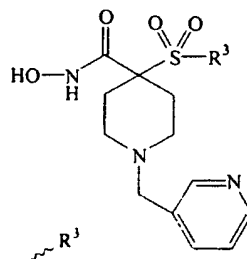


Table 139

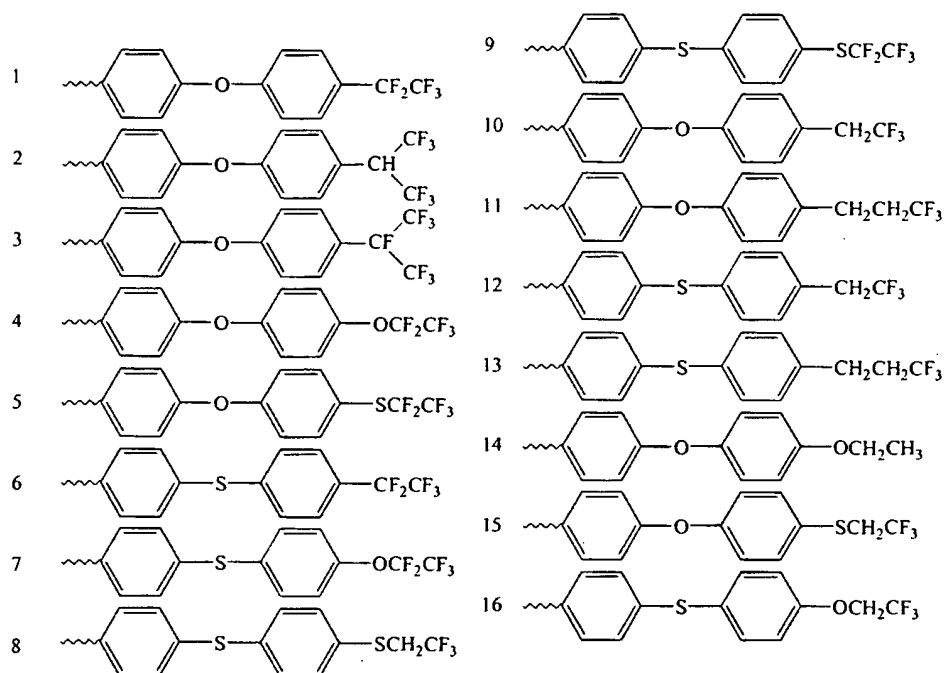
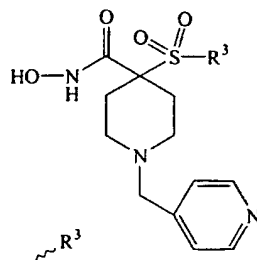


Table 140

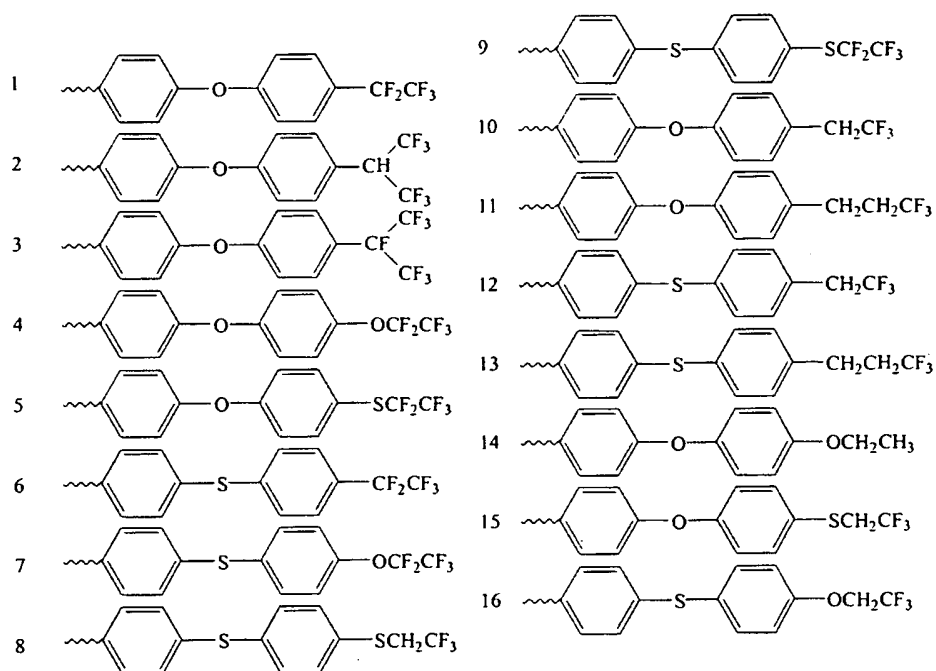
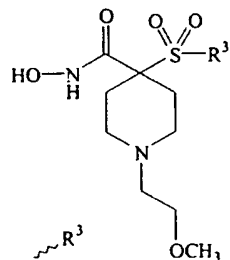


Table 141

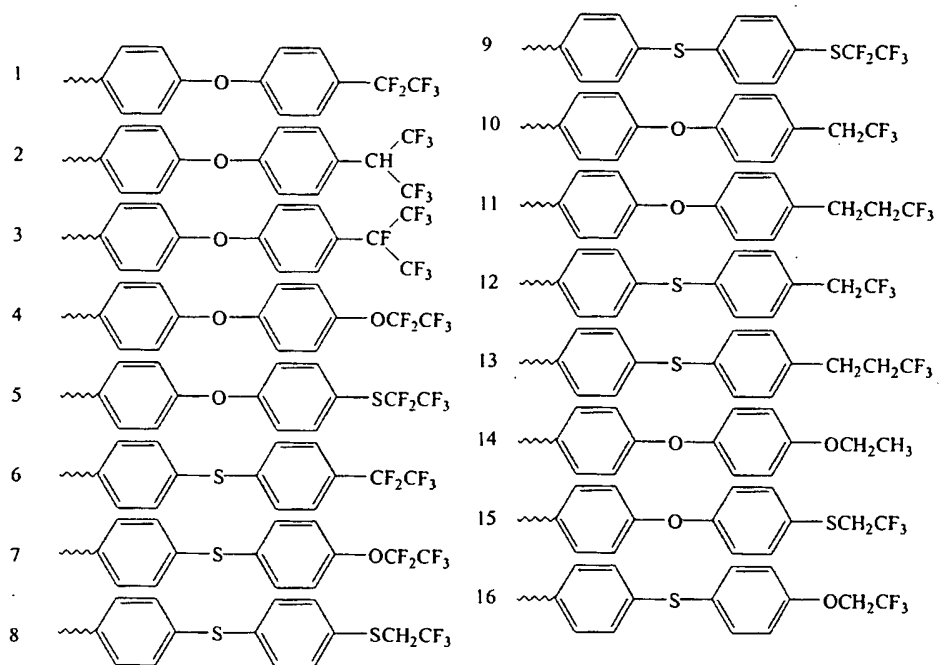
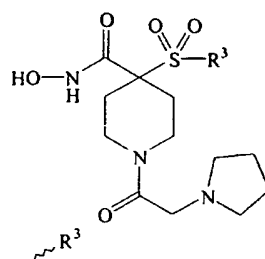
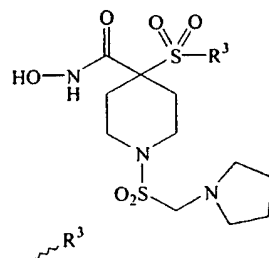
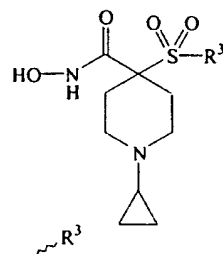


Table 142



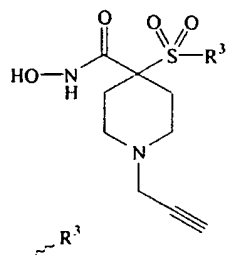
1		9	
2		10	
3		11	
4		12	
5		13	
6		14	
7		15	
8		16	

Table 143



1		7	
2		8	
3		9	
4		10	
5		11	
6		12	

Table 144



1		7	
2		8	
3		9	
4		10	
5		11	
6		12	

Table 145

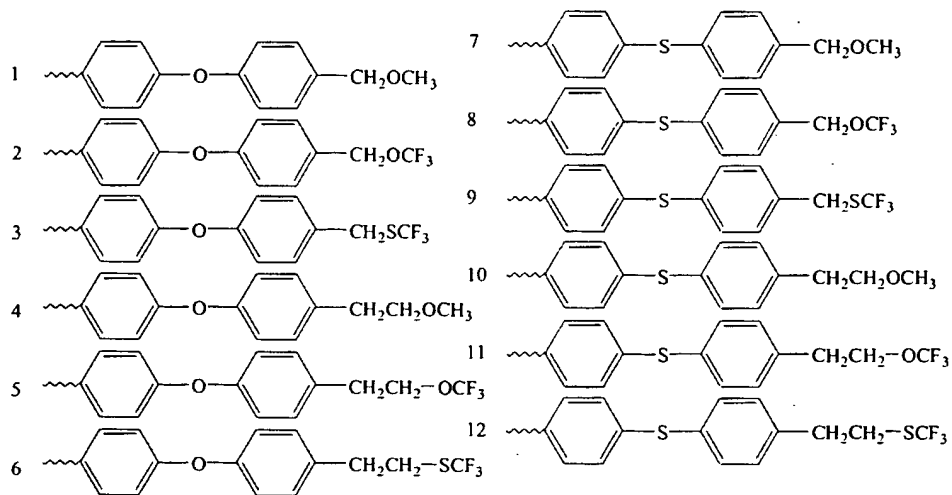
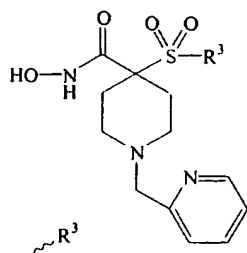


Table 146

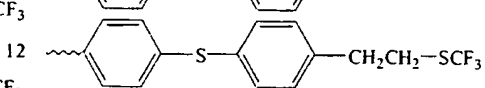
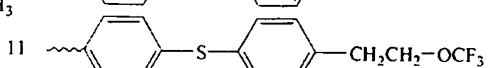
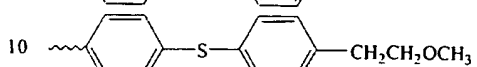
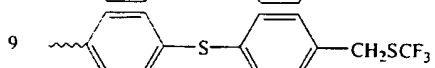
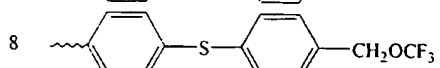
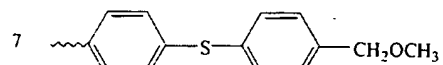
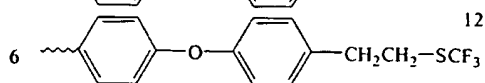
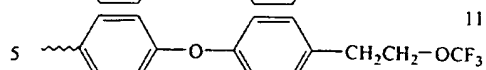
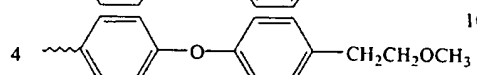
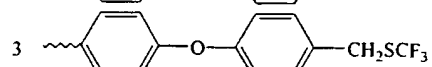
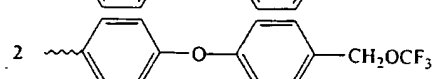
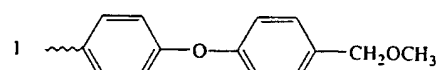
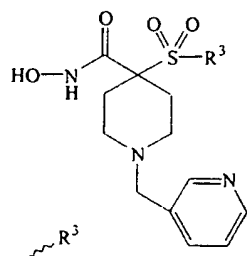
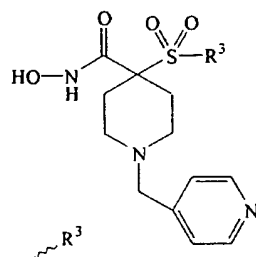


Table 147



1		7	
2		8	
3		9	
4		10	
5		11	
6		12	

Table 148

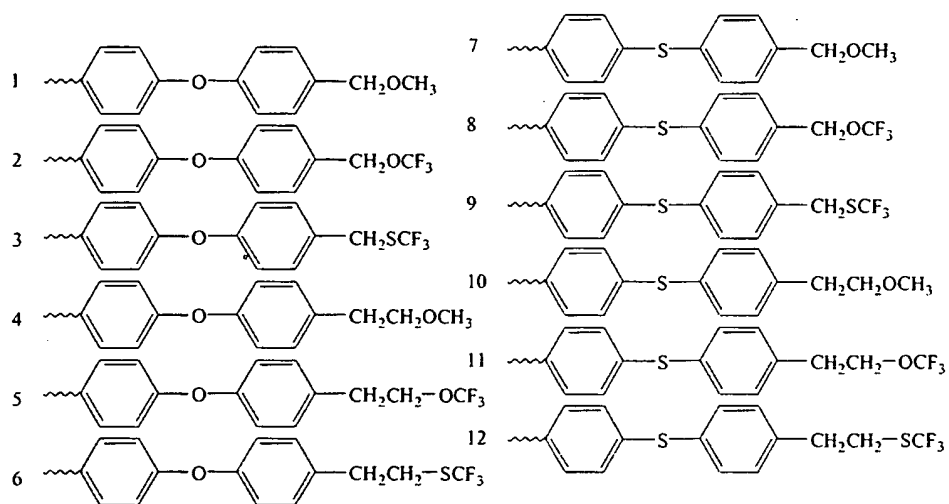
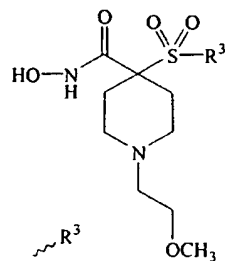
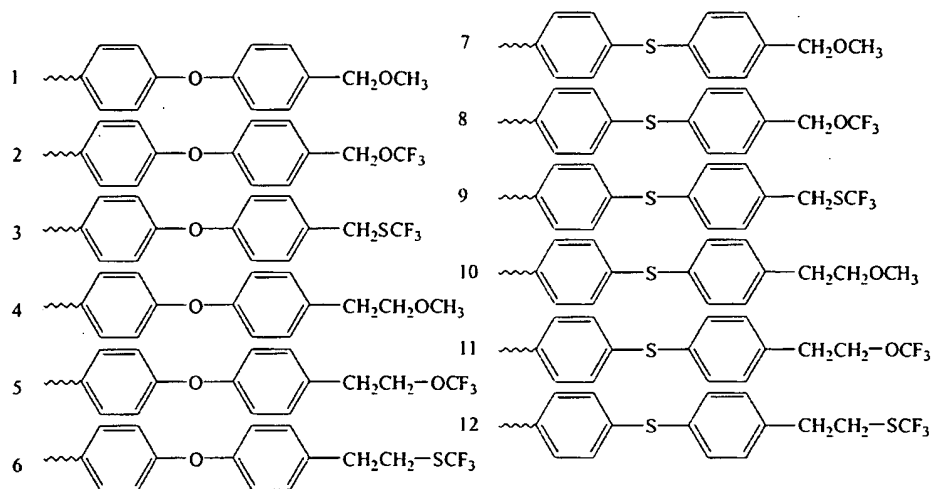
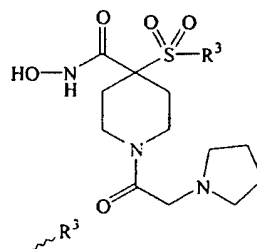
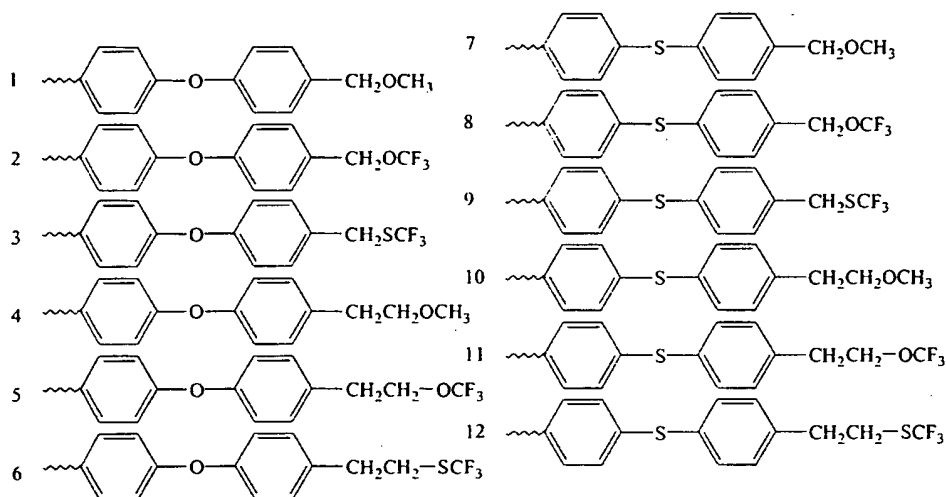
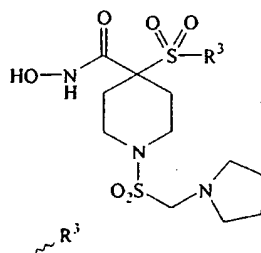


Table 149



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Table 150



5

A contemplated inhibitor compound is used for treating a host mammal such as a mouse, rat, rabbit, dog, horse, primate such as a monkey, chimpanzee or human that has a condition associated with pathological matrix metalloprotease activity.

Also contemplated is use of a contemplated metalloprotease inhibitor compound in the treatment of a disease state that can be affected by the activity of metalloproteases TNF- α convertase.

Exemplary of such disease states are the acute phase responses of shock and sepsis, coagulation responses, hemorrhage and cardiovascular effects, fever and inflammation, anorexia and cachexia.

5 In treating a disease condition associated with pathological matrix metalloproteinase activity, a contemplated MMP inhibitor compound can be used in the form of an amine salt derived from an inorganic or organic acid. Exemplary salts include but are not
10 limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate,
15 hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate,
20 picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate and undecanoate.

Also, a basic nitrogen-containing group can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl
25 chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and
30 others to provide enhanced water-solubility. Water or oil-soluble or dispersible products are thereby obtained as desired. The salts are formed by combining the basic compounds with the desired acid.

Other compounds useful in this invention that are acids can also form salts. Examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or
5 with organic bases or basic quaternary ammonium salts.

In some cases, the salts can also be used as an aid in the isolation, purification or resolution of the compounds of this invention.

10 Total daily dose administered to a host mammal in single or divided doses can be in amounts, for example, for 0.001 to 30 mg/kg body weight daily and more usually 0.01 to 10 mg. Dosage unit compositions can contain such amounts or submultiples
15 thereof to make up the daily dose. A suitable dose can be administered, in multiple sub-doses per day. Multiple doses per day can also increase the total daily dose, should this be desired by the person prescribing the drug.

20 The dosage regimen for treating a disease condition with a compound and/or composition of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of
25 the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound
30 is administered as part of a drug combination. Thus, the dosage regimen actually employed can vary widely and therefore can deviate from the preferred dosage regimen set forth above.

A compound of the present invention can be formulated as a pharmaceutical composition. Such a composition can then be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania; 1975 and Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as

oleic acid find use in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are sold at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration can include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, a contemplated aromatic sulfone hydroximate inhibitor compound can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can

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also comprise buffering agents such as sodium citrate, magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from carriers or granules having one or more of the carriers for oral administration. A contemplated aromatic sulfone hydroximate inhibitor compound can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

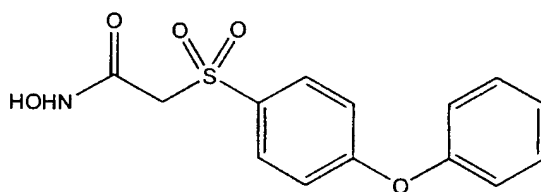
Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the mammalian host treated and the particular mode of administration.

Best Mode For Carrying Out The Invention

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific
5 embodiments are, therefore, to be construed as merely illustrative, and not limiting of the remainder of the disclosure in any way whatsoever.

Example 1: Preparation of N-hydroxy-2-[(4-
10 phenoxyphenyl)sulfonyl]acetamide



Part A: To a solution of 3-bromopyruvic
15 acid hydrate (1.95 g, 11.7 mmol) cooled to zero degrees Celsius in methanol (50 mL) was added 4-(phenoxy)benzenethiol (2.35 g, 11.7 mmol). The solution was stirred for 15 minutes followed by concentration in vacuo. The residue was partitioned
20 between ethyl acetate and H₂O and the organic layer was dried over magnesium sulfate. Concentration in vacuo provided the crude sulfide as a yellow solid that was used without any additional purification.

Part B: To a solution of the crude sulfide
25 of part A (1.2 g, <2.6 mmol) in methanol/H₂O cooled to zero degrees Celsius was added Oxone® (3.5 g, 5.72 mmol). The solution was stirred for 1 hour followed by removal of excess Oxone® by filtration. The

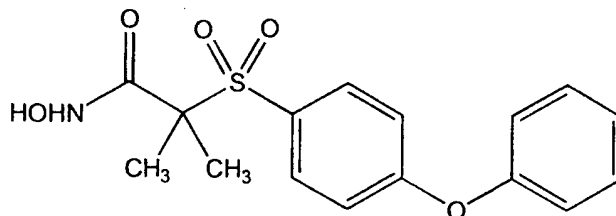
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filtrate was concentrated and the residue was dissolved into ethyl acetate and washed with saturated NaHCO_3 and saturated NaCl and dried over magnesium sulfate. After concentration in vacuo the
5 resulting residue was dissolved into methanol and thionyl chloride (1.9 mL, 26 mmol) was added. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone as a solid (350 mg, 44%). MS(CI) MH^+ calculated for $\text{C}_{15}\text{H}_{14}\text{O}_5\text{S}$: 307, found 307.

10 Part C: To a solution of the sulfone (350 mg, 1.1 mmol) in methanol (2 mL) and THF (THF; 2 mL) was added 50 percent aqueous hydroxylamine (1 mL). The solution was stirred overnight. Trituration with ethyl acetate provided the title compound as a white
15 solid (270 mg, 77%). HPLC purity: >97%. MS(CI) MH^+ calculated for $\text{C}_{14}\text{H}_{13}\text{NO}_5\text{S}$: 308, found 308.

Example 2: Preparation of N-hydroxy-2-methyl-2-[(4-
phenoxyphenyl)sulfonyl]propanamide

20



Part A: To a solution of 4-(
phenoxy)benzenethiol (3.8 g, 18.8 mmol) in methanol
25 (60 mL) cooled to zero degrees Celsius was added t-butyl bromoacetate (2.8 mL, 18.8 mmol) and triethylamine (2.6 mL, 19.0 mmol). The solution was

stirred for 30 minutes and was then concentrated in vacuo. The residue was partitioned between ethyl acetate and H₂O and the organic layer was washed with saturated NaCl and dried over magnesium sulfate.

5 Concentration in vacuo provided the sulfide as an oil. To a solution of the sulfide in dichloromethane (85 mL) was added m-chloroperbenzoic acid (13.8 g, 43.2 mmol) over 15 minutes. The solution was stirred at ambient temperature for 2 hours. The reaction was
10 quenched by the addition of aqueous Na₂SO₃. After 30 minutes the solution was filtered through Celite®. The filtrate was washed with 25 percent aqueous hydroxylamine, 1N HCl, and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica,
15 ethyl acetate/hexane) provided the sulfone as a white solid (4.0 g, 68%).

Part B: To a solution of the sulfone of part A (3.2 g, 9.2 mmol) in THF (65 mL) cooled to zero degrees Celsius was added sodium hydride (730 mg
20 of a 60 percent dispersion in mineral oil, 18.4 mmol). After 10 minutes, methyl iodide (2.28 mL, 36.8 mmol) was added dropwise and the mixture was stirred for 18 hours at ambient temperature. The reaction was quenched with H₂O and concentrated in
25 vacuo. The aqueous residue was diluted with ethyl acetate and the organic phase was washed with H₂O and dried over Na₂SO₄. Concentration in vacuo provided the dimethyl compound as an off-white solid (3.2 g, 92%). HPLC purity: 95%.

30 Part C: To a solution of the dimethyl compound of part B (3.2 g, 8.5 mmol) in anisole (10

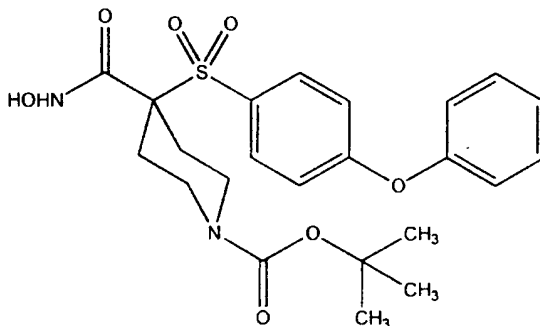
mL) was added trifluoroacetic acid (30 mL) and the solution was stirred for 30 minutes. Concentration in vacuo followed by trituration (ethyl ether) provided the acid as a white solid (750 mg, 28%).

- 5 HPLC purity: 99%. MS(CI) MH^+ calculated for $C_{16}H_{16}O_5S$: 321, found 321.

- Part D: To a solution of the acid of part C (723 mg, 2.26 mmol) in DMF (DMF; 4.5 mL) was added N-hydroxybenzotriazole• H_2O (HOBT; 366 mg, 2.71 mmol)
- 10 and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC; 476 mg, 2.49 mmol). After the solution was stirred for 1 hour at ambient temperature 50 percent aqueous hydroxylamine (0.40 mL, 6.8 mmol) was added. After 15 minutes the
- 15 solution was partitioned between ethyl acetate and H_2O . The organic layer was washed with H_2O and saturated NaCl and dried over Na_2SO_4 . Reverse phase chromatography (on silica, acetonitrile/ H_2O) provided the title compound as a white foam (434 mg, 57%).
- 20 HPLC purity: 99%. MS(CI) $M+Li^+$ calculated for $C_{16}H_{17}NO_5O$: 342, found 342.

- Example 3: Preparation of 1,1-dimethylethyl ester
- 4-[(hydroxyamino)carbonyl]-4-
- 25 [(phenoxyphenyl)-sulfonyl]-1-
- piperidinecarboxylic acid

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Part A: A solution of 4-(phenoxy)benzenethiol (2.03 g, 10.0 mmol) in DMSO (DMSO; 20 mL) was heated to sixty-five degrees Celsius for 5 hours. The solution remained at ambient temperature for 18 hours. The solution was extracted with ethyl acetate and the combined organic layers were washed with H₂O and saturated NaCl and dried over magnesium sulfate. Concentration in vacuo provided the disulfide as a yellow oil (2.3 g, quantitative yield).

Part B: To a solution of ethyl isonipecotate (15.7 g, 0.1 mol) in THF (100 mL) was added a solution of di-tert-butyl dicarbonate (21.8 g, 0.1 mol) in THF (5 mL) dropwise over 20 minutes. The solution was stirred overnight at ambient temperature and concentrated in vacuo to yield a light oil. The oil was filtered through silica gel (7:3 ethyl acetate/hexanes) and concentrated in vacuo to give the BOC-piperidine compound (26.2 g, quantitative yield) as a clear, colorless oil.

Part C: To a solution of diisopropylamine (2.8 mL, 20 mmol) in THF (30 mL), cooled to minus seventy-eight degrees Celsius, was added n-butyl lithium (12.5 mL, 20 mmol) dropwise. After 15

minutes, the BOC-piperidine compound of part B (2.6 g, 10 mmol) in THF (10 mL) was added dropwise. After 1.5 hours the solution was cooled to minus sixty degrees Celsius and the disulfide of part A (2.0 g, 10 mmol) in THF (7 mL). The solution was stirred at ambient temperature for 2 hours. The solution was diluted with H₂O and extracted with ethyl acetate. The organic layer was washed with H₂O and saturated NaCl and dried over magnesium sulfate.

10 Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as an oil (1.8 g, 40%).

Part D: To a solution of the sulfide of part C (1.8 g, 3.95 mmol) in dichloromethane (75 mL) cooled to zero degrees Celsius, was added m-chloroperbenzoic acid (1.7 g, 7.9 mmol). The solution was stirred for 1.5 hours followed by dilution with H₂O and extraction with dichloromethane. The organic layer was washed with 10 percent Na₂SO₄, H₂O, and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone as a solid (1.15 g, 59%).

15 20

Part E: To a solution of the sulfone of part D (800 mg, 1.63 mmol) in THF (9 mL) and ethanol (9 mL) was added NaOH (654 mg, 16.3 mmol) in H₂O (3 mL). The solution was heated at sixty-five degrees Celsius for 18 hours. The solution was concentrated in vacuo and the residue was dissolved in H₂O. Following acidification with 2N HCl to pH 4, the solution was extracted with ethyl acetate and the organic layer was washed with saturated NaCl and

25 30

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dried over magnesium sulfate. Concentration in vacuo provided the acid as a white foam (790 mg, quantitative yield). Analytical calculated for $C_{23}H_{27}NO_7S$: C, 59.86; H, 5.90; N, 3.04; S, 6.95. Found:

5 C, 59.49; H, 6.37; N, 2.81; S, 6.59.

Part F: To a solution of the acid of part G (730 mg, 1.58 mmol) in DMF (9 mL) was added HOBT (256 mg, 1.90 mmol) followed by EDC (424 mg, 2.21 mmol), 4-methylmorpholine (0.521 mL, 4.7 mmol) and 50

10 percent aqueous hydroxylamine (1.04 mL, 15.8 mmol). The solution was stirred for 20 hours and additional N-hydroxybenzotriazole•H₂O (256 mg), EDC (424 mg) and 50 percent aqueous hydroxylamine (1.04 mL) were added. After an additional 24 hours of stirring the solution

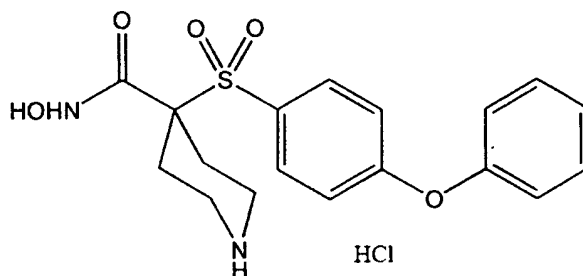
15 was diluted with H₂O and extracted with ethyl acetate and the organic layer was washed with saturated NaCl and dried over magnesium sulfate. Reverse phase chromatography (on silica, acetonitrile/H₂O) provided the title compound as a white solid (460 mg, 61%).

20 HPLC purity: >99%. Analytical calculated for $C_{23}H_{28}N_2O_7S$: C, 57.97; H, 5.92; N, 5.88; S, 6.73. Found: C, 57.95; H, 6.02; N, 5.81; S, 6.85.

Example 4: Preparation of N-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-4-piperidinecarboxamide,

25 monohydrochloride

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Part A: A solution of 4-(phenoxy)benzenethiol (2.03 g, 10.0 mmol) in DMSO (20 mL) was heated to sixty-five degrees Celsius for 5 hours. The solution remained at ambient temperature for 18 hours. The solution was extracted with ethyl acetate and the combined organic layers were washed with H₂O and saturated NaCl and dried over magnesium sulfate. Concentration in vacuo provided the disulfide as a yellow oil (2.3 g, quantitative yield).

Part B: To a solution of ethyl isonipecotate (15.7 g, 0.1 mol) in THF (100 mL) was added a solution of di-tert-butyl dicarbonate (21.8 g, 0.1 mol) in THF (5 mL) dropwise over 20 minutes. The solution was stirred overnight at ambient temperature and concentrated in vacuo to yield a light oil. The oil was filtered through silica gel (on silica, ethyl acetate/hexane) and concentrated in vacuo to give the BOC-piperidine compound as a clear, colorless oil (26.2 g, quantitative yield).

Part C: To a solution of diisopropylamine (2.8 mL, 20 mmol) in THF (30 mL), cooled to minus seventy-eight degrees Celsius, was added n-butyl lithium (12.5 mL, 20 mmol) dropwise. After 15

minutes, the BOC-piperidine compound of part B (2.6 g, 10 mmol) in THF (10 mL) was added dropwise. After 1.5 hours the solution was cooled to minus 60 degrees Celsius and the disulfide of part A (2.0 g, 10 mmol) in THF (7 mL) was added. The solution was stirred at ambient temperature for 2 hours. The solution was diluted with H₂O and extracted with ethyl acetate. The organic layer was washed with H₂O and saturated NaCl and dried over magnesium sulfate.

10 Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as an oil (1.8 g, 40%).

Part D: To a solution of the sulfide of part C (1.8 g, 3.95 mmol) in dichloromethane (75 mL) cooled to zero degrees C, was added m-chloroperbenzoic acid (1.7 g, 7.9 mmol). The solution was stirred for 1.5 hours followed by dilution with H₂O and extraction with dichloromethane. The organic layer was washed with 10 percent Na₂SO₃, H₂O, and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone as a solid (1.15 g, 59%).

Part E: To a solution of the sulfone of part D (800 mg, 1.63 mmol) in THF (9 mL) and ethanol (9 mL) was added NaOH (654 mg, 16.3 mmol) in H₂O (3 mL). The solution was heated at sixty-five degrees Celsius for 18 hours. The solution was concentrated in vacuo and the residue was dissolved in H₂O. Following acidification with 2N HCl to pH 4, the solution was extracted with ethyl acetate and the organic layer was washed with saturated NaCl and

dried over magnesium sulfate. Concentration in vacuo provided the acid as a white foam (790 mg, quantitative yield). analytical calculated for $C_{23}H_{27}NO_5S$: C, 59.86; H, 5.90; N, 3.04; S, 6.95. Found: 5 C, 59.49; H, 6.37; N, 2.81; S, 6.59.

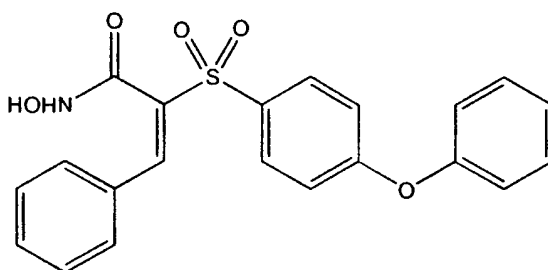
Part F: To a solution of the acid of part G (730 mg, 1.58 mmol) in DMF (9 mL) was added HOBT (256 mg, 1.90 mmol) followed by EDC (424 mg, 2.21 mmol), 4-methylmorpholine (0.521 mL, 4.7 mmol) and 50 percent aqueous hydroxylamine (1.04 mL, 15.8 mmol). The solution was stirred for 20 hours and additional HOBT (256 mg), EDC (424 mg) and 50 percent aqueous hydroxylamine (1.04 mL) were added. After an additional 24 hours of stirring the solution was diluted with H_2O , and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over magnesium sulfate. Reverse phase HPLC (acetonitrile/ H_2O) provided the hydroxamate as a white solid (460 mg, 61%). HPLC purity: >99%. analytical 20 calculated for $C_{23}H_{28}N_2O_5S$: C, 57.97; H, 5.92; N, 5.88; S, 6.73. Found: C, 57.95; H, 6.02; N, 5.81; S, 6.85.

Part G: Into a solution of the hydroxamate of part F (385 mg, 0.808 mmol) in ethyl acetate (25 mL), cooled to zero degrees Celsius, was bubbled HCl 25 gas for 5 minutes. After standing for 30 minutes, the solution was concentrated in vacuo. Trituration with ethyl ether provided the title compound as a white solid (330 mg, quantitative yield). MS(CI) MH^+ calculated for $C_{18}H_{20}N_2O_5S$: 377, found 377. HRMS 30 calculated for $C_{18}H_{20}N_2O_5S$: 377.1171, found 377.1170. analytical calculated for $C_{18}H_{20}N_2O_5S \cdot 1.1HCl \cdot 0.25H_2O$: C,

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51.35; H, 5.17; N, 6.65; S, 7.62; Cl, 9.26. Found: C, 51.58; H, 5.09; N, 6.55; S, 8.02; Cl, 9.09.

Example 5: Preparation of (E) N-hydroxy-2-
5 [(4-phenoxyphenyl)sulfonyl]-3-
phenyl-2-propenamide



10 Part A: To a solution of 4-(phenoxy)benzenethiol (5.00 g, 24.7 mmol) in methanol (100 mL) cooled to zero degrees Celsius was added t-butylbromoacetate (3.99 mL, 24.7 mmol). Following the addition of triethylamine (3.60 mL, 25.8 mmol)
15 the solution was stirred for 40 minutes. The solution was concentrated in vacuo and the resulting residue was dissolved in ethyl acetate and washed with H₂O and saturated NaCl and dried over Na₂SO₄. Concentration in vacuo provided the sulfide as an oil
20 (7.9 g, quantitative yield).

Part B: To a solution of the sulfide of part A (7.9 g, 24.7 mmol) in methanol (180 mL) and H₂O (20 mL) was added Oxone® (38.4 g, 62.5 mmol) and the mixture was stirred for 22 hours. The mixture was
25 acidified to pH 4 with 2.5N NaOH and decanted to remove insoluble salts. The decantate was

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concentrated to one-half volume and partitioned between ethyl acetate and H₂O. The organic layer was washed with H₂O and saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone as a yellow solid (5.79 g, 67%).

Part C: To a solution of the sulfone of part B (2.5064 g, 7.20 mmol) and benzaldehyde (0.748 mL, 7.36 mmol) in benzene (20 mL) were added acetic acid (0.15 mL) and piperidine (0.05 mL). The solution was heated to reflux for 2 hours and the condensate was collected via a Dean-Stark trap. After an additional 1.5 hours of reflux, the solution was returned to ambient temperature and stirred for 18 hours. The solution was diluted with ethyl acetate and washed with H₂O and saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) followed by trituration (ethyl ether/hexane) provided the unsaturated sulfone as a white solid (1.97 g, 73%). HPLC purity: >98%.

Part D: Into a solution of the unsaturated sulfone of part C (0.5053 g, 1.16 mmol) was bubbled HCl gas for 1 hour. The solution was concentrated in vacuo and the residue was dissolved into ethyl acetate and washed with H₂O and dried over Na₂SO₄. Concentration in vacuo provided the acid as an oil (0.41 g, 93%).

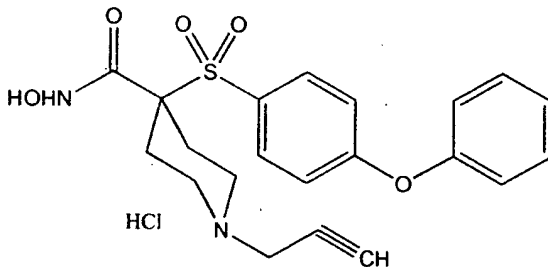
Part E: To a solution of the acid of part D (461 mg, 1.21 mmol) was added thionyl chloride (3.0 mL) and the solution was heated to one hundred degrees Celsius for 1 hour. Concentration in vacuo

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provided the acid chloride as an amber oil (380 mg, 79%).

Part F: To a solution of the acid chloride of part E (380 mg, 0.95 mmol) in THF (20 mL) was
5 added 50 percent aqueous hydroxylamine (1.7 mL, 9.5 mmol). The solution was stirred at zero degrees Celsius for 1 hour. The solution was diluted with ethyl acetate, washed with H₂O and saturated NaCl, and dried over Na₂SO₄. Reverse phase chromatography (on
10 silica, acetonitrile/H₂O) followed by trituration (ethyl ether/hexane) provided the title compound as a white solid (131 mg, 35%). HPLC purity: >97%.

Example 6: Preparation of N-hydroxy-4-[(4-
15 phenoxyphenyl)sulfonyl]-1-(2-propynyl)-4-
piperidinecarboxamide, monohydrochloride



20 Part A: A solution of 4-(phenoxy)benzenethiol (2.03 g, 10.0 mmol) in DMSO (20 mL) was heated to 65 degrees Celsius for 5 hours. The solution remained at ambient temperature for 18 hours. The solution was extracted with ethyl acetate and the combined
25 organic layers were washed with H₂O and saturated NaCl, and dried over magnesium sulfate.

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Concentration in vacuo provided the disulfide as a yellow oil (2.3 g, quantitative yield).

Part B: To a solution of ethyl isonipecotate (15.7 g, 0.1 mol) in THF (100 mL) was
5 added a solution of di-tert-butyl dicarbonate (21.8 g, 0.1 mol) in THF (5 mL) dropwise over 20 minutes. The solution was stirred overnight at ambient temperature and concentrated in vacuo to yield a light oil. The oil was filtered through silica gel
10 (ethyl acetate/hexane) and concentrated in vacuo to give the BOC-piperidine compound as a clear, colorless oil (26.2 g, quantitative yield).

Part C: To a solution of diisopropylamine (2.8 mL, 20 mmol) in THF (30 mL), cooled to minus
15 seventy-eight degrees Celsius, was added n-butyl lithium (12.5 mL, 20 mmol) dropwise. After 15 minutes, the BOC-piperidine compound of part B (2.6 g, 10 mmol) in THF (10 mL) was added dropwise. After 1.5 hours the solution was cooled to minus sixty
20 degrees Celsius and the disulfide of part A (2.0 g, 10 mmol) in THF (7 mL) was added. The solution was stirred at ambient temperature for 2 hours. The solution was diluted with H₂O and extracted with ethyl acetate. The organic layer was washed with H₂O and
25 saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as an oil (1.8 g, 40%).

Part D: To a solution of the sulfide of part C (1.8 g, 3.95 mmol) in dichloromethane (75 mL)
30 cooled to zero degrees Celsius, was added m-chloroperbenzoic acid (1.7 g, 7.9 mmol). The

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solution was stirred for 1.5 hours followed by dilution with H₂O and extraction with dichloromethane. The organic layer was washed with 10 percent Na₂SO₄, H₂O, and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone as a solid (1.15 g, 59%).

Part E: Into a solution of the sulfone of part D (3.56 g, 7.0 mmol) in ethyl acetate (100 mL) cooled to zero degrees Celsius was bubbled HCl gas for 5 minutes. Concentration in vacuo followed by trituration with ethyl ether provided the amine hydrochloride salt as a white solid (3.5 g, quantitative yield). MS(CI) MH⁺ calculated for C₂₀H₂₃NO₃S: 390, found 390.

Part F: To a solution of the amine hydrochloride salt of part E (2.6 g, 6 mmol) and K₂CO₃ (1.66 g, 12 mmol) in DMF (50 mL) was added propargyl bromide (892 mg, 6 mmol) and the solution was stirred at ambient temperature for 4 hours. The solution was diluted with H₂O and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the propargyl amine as a white solid (2.15 g, 82%).

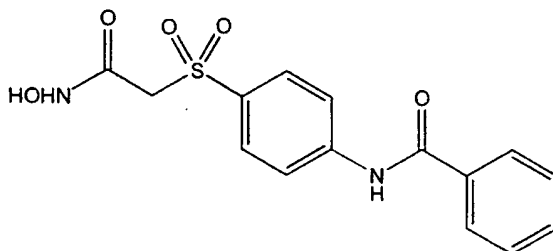
Part G: To a solution of the propargyl amine of part F (2.15 g, 5 mmol) in THF (30 mL) and ethanol (30 mL) was added NaOH (2.0 g, 50 mmol) and the solution was heated at 65 degrees Celsius for 48 hours. The solution was concentrated in vacuo and

the aqueous residue was acidified to a pH value of 5. Vacuum filtration of the resulting precipitate provided the acid as a white solid (2.04 g, quantitative yield).

5 Part H: To a solution of the acid of part G (559 mg, 1.4 mmol) in dichloromethane (5 mL) was added triethylamine (0.585 mL, 4.2 mmol) and 50 percent aqueous hydroxylamine (0.925 mL, 14.0 mmol) followed by bromotris(pyrrolidino)phosphonium
10 hexafluorophosphate (PyBroP®; 718 mg, 1.54 mmol). The solution was stirred at ambient temperature for 4 hours. The solution was diluted with H₂O and extracted with dichloromethane. The organic layer was washed with saturated NaCl and dried over
15 magnesium sulfate. Reverse phase chromatography (on silica, acetonitrile/H₂O) provided the hydroxamate as a white solid (140 mg, 25%). Analytical calculation for C₂₁H₂₂N₂O₅S: C, 60.85; H, 5.37; N, 6.76; S, 7.74. Found: C, 60.47; H, 5.35; N, 6.61; S, 7.46.

20 Part I: To a solution of the hydroxamate of part H (121 mg, 0.292 mmol) in methanol (2 mL) cooled to zero degrees Celsius was added acetyl chloride (0.228 mL, 0.321 mmol) in methanol (1 mL). After stirring at ambient temperature for 30 minutes
25 the solution was concentrated under a stream of N₂. Trituration with ethyl ether provided the title compound as a white solid (107 mg, 81%). Analytical calculation for C₂₁H₂₂N₂O₅S•HCl•0.3H₂O: C, 55.27; H, 5.21; N, 6.14. Found: C, 54.90; H, 5.37; N, 6.07.

Example 7: Preparation of N-[4-[[2-(hydroxyamino)-2-
oxoethylsulfonyl]]phenyl]benzamide



5

Part A: To a suspension of 2-(4-aminophenylthio)acetic acid (20.00 g, 0.109 mmol) in methanol (100 mL) cooled to zero degrees Celsius was added thionyl chloride (24.0 mL, 0.327 mmol) dropwise. Additional methanol was added (100 mL) and the suspension was heated to reflux for 2 hours. The solution was concentrated in vacuo and the residue was dissolved into H₂O and neutralized with saturated NaHCO₃. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with saturated NaCl and dried over Na₂SO₄. Concentration in vacuo provided the methyl ester as a dark purple oil (22.75 g, quantitative yield). HPLC purity: 99%.

Part B: To a solution of the methyl ester of part A (5.00 g, 25.35 mmol) and triethylamine (7.07 mL, 50.70 mmol) in dichloromethane (50 mL) was added benzoyl chloride (3.24 mL, 27.89 mmol) and the solution was stirred at ambient temperature for 2 hours. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate, THF and H₂O. The organic layer was washed with H₂O

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and saturated NaCl and dried over Na₂SO₄.

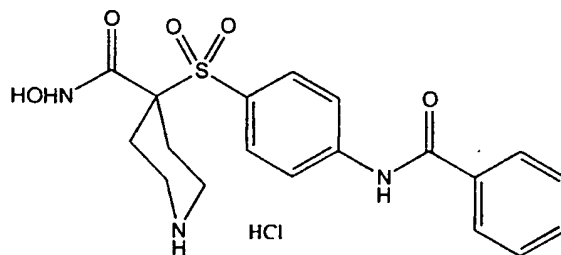
Concentration in vacuo provided the benzamide as a purple solid (7.06 g, 92%). HPLC purity: 98%. MS(CI) M+Li⁺ calculated for C₁₆H₁₅NO₃S: 308, found 308.

5 Part C: To a solution of the benzamide of part B (4.00 g, 13.27 mmol) in THF (100 mL) and H₂O (10 mL) cooled to zero degrees Celsius was added Oxone® (potassium monopersulfate; 24.47 g, 39.81 mmol). The slurry was stirred overnight (about
10 eighteen hours) at ambient temperature. The mixture was filtered to remove excess Oxone® and the filtrate was concentrated in vacuo. The residue was dissolved into ethyl acetate and washed with H₂O and saturated NaCl, and then dried over Na₂SO₄. Concentration in
15 vacuo provided the sulfone as a pink solid (4.11 g, 93%). HPLC purity: 98%. MS(CI) M+Li⁺ calculated for C₁₆H₁₅NO₅S: 340, found 340.

 Part D: To a solution of the sulfone of part C (400 mg, 1.2 mmol) in THF (9 mL) was added 50
20 percent aqueous hydroxylamine (5.0 mL). The solution was stirred for 8 hours and was concentrated in vacuo. Trituration with hot ethyl ether provided the title compound as an off-white solid (348 mg, 78%). HPLC purity: 97%. MS(CI) MH⁺ calculated for C₁₇H₁₄N₂O₅S:
25 335, found 335.

Example 8: Preparation of N-[4-[[2-(hydroxyamino)-2-oxo-1-(piperidin-4-yl)ethyl]sulfonyl]-phenyl]-benzamide, monohydrochloride

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Part A: To a solution of diethanolamine (22.16 g, 0.211 mol) in THF (100 mL) cooled to zero
5 degrees Celsius was added di-*t*-butyl dicarbonate (46.0 g, 0.211 mol) and the solution was stirred at ambient temperature for 20 hours. The solution was concentrated in vacuo and the resulting residue was filtered through a silica pad (5 percent methanol/95
10 percent dichloromethane) to provide the diol as a clear oil (45.06 g, quantitative yield). MS(CI) MH^+ calculated for $C_9H_{11}O_4S$: 206, found 206.

Part B: To a suspension of 2-(4-aminophenylthio)acetic acid (20.00 g, 0.109 mmol) in
15 methanol (100 mL) cooled to zero degrees Celsius thionyl chloride (24.0 mL, 0.327 mmol) was added dropwise. After additional methanol was added (100 mL), the suspension was heated to reflux for 2 hours. The composition was concentrated in vacuo, the
20 residue was dissolved in H_2O and neutralized with saturated $NaHCO_3$. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with saturated NaCl and dried over Na_2SO_4 . Concentration in vacuo provided the methyl ester as a
25 dark purple oil (22.75 g, quantitative yield). HPLC purity: 99%.

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Part C: To a solution of the methyl ester of part B (5.00 g, 25.35 mmol) and triethylamine (7.07 mL, 50.70 mmol) in dichloromethane (50 mL) was added benzoyl chloride (3.24 mL, 27.89 mmol) and the solution was stirred at ambient temperature for 2 hours. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate, THF and H₂O. The organic layer was washed with H₂O and saturated NaCl and dried over Na₂SO₄. Concentration in vacuo provided the benzamide as a purple solid (7.06 g, 92%). HPLC purity: 98%.

Part D: To a solution of the benzamide of part C (4.00 g, 13.27 mmol) in THF (100 mL) and H₂O (10 mL) cooled to zero degrees Celsius was added Oxone® (24.47 g, 39.81 mmol). The slurry was stirred overnight (about eighteen hours) at ambient temperature. The mixture was filtered to remove excess Oxone® and the filtrate was concentrated in vacuo. The residue was dissolved into ethyl acetate and washed with H₂O and saturated NaCl and dried over Na₂SO₄. Concentration in vacuo provided the sulfone as a pink solid (4.11 g, 93%). HPLC purity: 98%.

Part E: To a solution of the diol of part A (1.03 g, 5.00 mmol) and the methyl ester of part D (2.00 g, 6.00 mmol) in THF (100 mL) was added the 1,1'-(azodicarbonyl)dipiperidine (5.05 g, 20.00 mmol). To this slurry was added trimethyl phosphine (20.00 mL of a 1.0M solution in THF, 20.00 mmol). The mixture stirred for 1 hour at ambient temperature and then was heated at 40 degrees Celsius for 18 hours. After the slurry returned to ambient

temperature, ethyl ether was added and the insoluble solids were removed by filtration. The filtrate was concentrated in vacuo and the resulting residue was dissolved into ethyl acetate, washed with H₂O and saturated NaCl, and then dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) provided the piperidine compound as a yellow solid (600 mg, 24%). MS(CI) MH⁺ calculated for C₂₅H₃₀N₂O₇S: 503, found 503.

10 Part F: To a solution of the piperidine compound of part E (950 mg, 1.89 mmol) in THF (10 mL) was added potassium silanolate (970 mg, 7.56 mmol) and the solution was stirred at ambient temperature for 72 hours. The solution was diluted with H₂O, acidified to pH 2 with 1M HCl, and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na₂SO₄. Concentration in vacuo provided the acid as a yellow solid (772 mg, 84%).

20 Part G: To a solution of the acid of part F (772 mg, 1.48 mmol) in DMF (9 mL) was added HOBT (240 mg, 1.77 mmol), 4-methylmorpholine (0.488 mL, 4.44 mmol), O-tetrahydropyranyl hydroxyamine (538 mg, 4.54 mmol) and EDC (397 mg, 2.07 mmol). The solution stirred at ambient temperature for 2 hours. Following concentration in vacuo the residue was partitioned between ethyl acetate and H₂O. The organic layer was washed with saturated NaCl and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxylamine as a white solid (608 mg, 70%). HPLC purity: >99%.

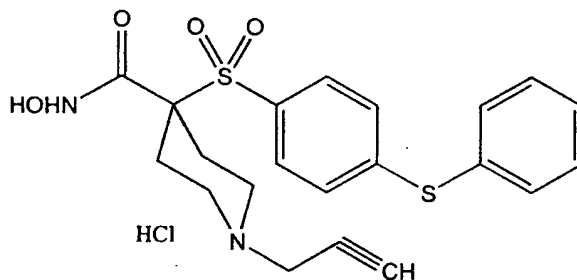
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Part H: To a solution of the protected hydroxylamine of part G (596 g, 1.01 mmol) in dioxane (3 mL) and methanol (1 mL) was added 4M HCl in dioxane (2.50 mL, 10.14 mmol) and the solution
5 stirred for 50 minutes at ambient temperature. Trituration with ethyl ether provided the title compound as a white solid (433 mg, 98%). HPLC purity: 98%. MS(CI) MH^+ calculated for $C_{19}H_{21}N_3O_5S$: 404, found 404.

10

Example 9: Preparation of N-hydroxy-4-
[[4-(phenylthio)phenyl]sulfonyl]-1-
(2-propynyl)-4-piperidinecarboxamide,
monohydrochloride

15



Part A: To a solution of ethyl isonipecotate (15.7 g, 0.1 mol) in THF (100 mL) was added a
20 solution of di-tert-butyl dicarbonate (21.8 g, 0.1 mol) in THF (5 mL) dropwise over 20 minutes. The solution was stirred overnight (about eighteen hours) at ambient temperature and concentrated in vacuo to yield a light oil. The oil was filtered through
25 silica gel (ethyl acetate/hexanes) and concentrated

in vacuo to give the BOC-piperidine compound as a clear, colorless oil (26.2 g, quantitative yield).

Part B: A solution of 4-fluorothiophenol (50.29 g, 390 mmol) in DMSO (500 mL) was heated to 65
5 degrees Celsius for 6 hours. The reaction was quenched into wet ice and the resulting solid was collected by vacuum filtration to provide the disulfide as a white solid (34.4 g, 68.9%).

Part C: To a solution of the BOC-piperidine
10 compound of part A (16 g, 62 mmol) in THF (300 mL) cooled to minus 50 degrees Celsius was added lithium diisopropylamide (41.33 mL, 74 mmol) and the solution was stirred for 1.5 hours at zero degrees Celsius. To this solution was added the disulfide of part B
15 (15.77 g, 62 mmol), and the resulting solution was stirred at ambient temperature for 20 hours. The reaction was quenched with the addition of H₂O and the solution was concentrated in vacuo. The aqueous residue was extracted with ethyl acetate and the
20 organic layer was washed with 0.5N KOH, H₂O, and saturated NaCl. Chromatography (on silica, hexane/ethyl acetate) provided the sulfide as an oil (18.0 g, 75%).

Part D: To a solution of the sulfide of
25 part C (16.5 g, 43 mmol) in dichloromethane (500 mL) cooled to zero degrees Celsius was added 3-chloroperbenzoic acid (18.0 g, 86 mmol) and the solution was stirred for 20 hours. The solution was diluted with H₂O and extracted with dichloromethane.
30 The organic layer was washed with 10 percent Na₂SO₃, H₂O, and saturated NaCl and dried over magnesium

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sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone as a solid (10.7 g, 60%).

Part E: Into a solution of the sulfone of
5 part D (10 g, 24.0 mmol) in ethyl acetate (250 mL)
was bubbled HCl gas for 10 minutes followed by
stirring at ambient temperature for 4 hours.
Concentration in vacuo provided the amine
hydrochloride salt as a white solid (7.27 g, 86%).

10 Part F: To a solution of the amine
hydrochloride salt of part E (5.98 g, 17.0 mmol) in
DMF (120 mL) was added potassium carbonate (4.7 g,
34.0 mmol) followed by propargyl bromide (2.02 g,
17.0 mmol) and the solution was stirred for 4 hours
15 at ambient temperature. The solution was partitioned
between ethyl acetate and H₂O, and the organic layer
was washed with H₂O and saturated NaCl and dried over
magnesium sulfate. Chromatography (on silica, ethyl
acetate/hexane) provided the propargyl amine as a
20 yellow oil (5.2 g, 86%).

Part G: To a solution of the propargyl
amine of part F in DMF (15 mL) was added thiophenol
(0.80 mL, 7.78 mmol) and CsCO₃ (2.79 g, 8.56 mmol) and
the solution was heated to 70 degrees Celsius for 6
25 hours. The solution was partitioned between ethyl
ether and H₂O. The organic layer was washed with H₂O
and saturated NaCl, and dried over magnesium sulfate.
Chromatography (on silica, ethyl acetate/hexane)
provided the S-phenoxyphenyl compound as an oil (1.95
30 g, 56%).

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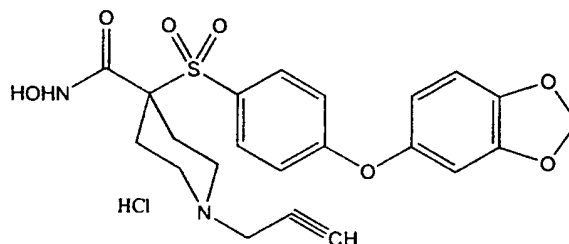
Part H: To a solution of the S-phenoxyphenyl of part G (1.81 g, 4.06 mmol) in ethanol (21 mL) and H₂O (3.5 mL) was added KOH (1.37 g, 24.5 mmol) and the solution was heated to 105
5 degrees Celsius for 4.5 hours. The solution was acidified to a pH value of 1 with concentrated HCl solution and then concentrated to provide the acid as a yellow residue that was used without additional purification (1.82 g).

10 Part I: To a solution of the acid of part H (1.82 g, 4.06 mmol) in acetonitrile (20 mL) was added O-tetrahydro-2H-pyran-2-yl-hydroxylamine (723 mg, 6.17 mmol) and triethylamine (0.67 mL, 4.86 mmol). To this stirring solution was added EDC (1.18
15 g, 6.17 mmol) and the solution was stirred for 18 hours. The solution was partitioned between H₂O and ethyl acetate. The organic layer was washed with H₂O, saturated NaHCO₃ and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl
20 acetate/hexane) provided the protected hydroxamate as a white solid (1.32 g, 63%).

Part J: To a solution of the protected hydroxamate of part I (9.65 g, 18.7 mmol) in methanol (148 mL) cooled to zero degrees Celsius was added
25 acetyl chloride (4.0 mL, 56.2 mmol), and the solution was stirred for 45 minutes at ambient temperature. Concentration in vacuo followed by trituration with ethyl ether provided the title compound as a white solid (8.10 g, 94%). MS(CI) MH⁺ calculated for
30 C₂₁H₂₂N₂O₄S₂: 431, found 431.

Example 10: Preparation of 4-[[4-(1,3-benzodioxol-5-yloxy)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride

5



Part A: To a solution of the propargyl amine of Example 9, part F (7.0 g, 19.8 mmol) in DMF
10 (30 mL) were added sesamol (5.52 g, 40 mmol) and potassium carbonate (5.52 g, 40 mmol), and the solution was heated to 85 degrees Celsius for 48 hours. The solution was partitioned between ethyl acetate and H₂O. The organic layer was dried over
15 magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as an oil (9.38 g, quantitative yield).

Part B: To a solution of the sulfide of part A (2.72 g, 5.92 mmol) in ethanol (30 mL) and H₂O
20 (5 mL) was added potassium hydroxide (2.0 g, 36 mmol) and the solution was heated to reflux for 4 hours. The solution was acidified to pH=3 with concentrated HCl. The solution was concentrated in vacuo and the residue was dissolved in acetonitrile (30 mL). To
25 this solution was added O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.05 g, 9.0 mmol), triethylamine (1 mL) and EDC (1.72 g, 9.0 mmol) and the solution was

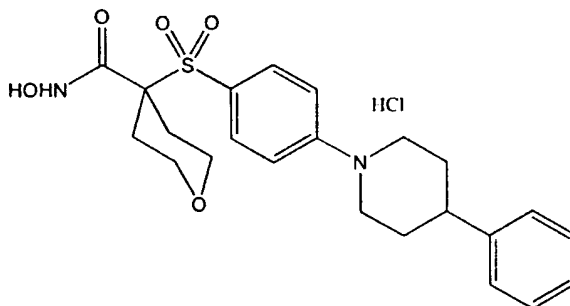
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stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and diluted with saturated NaHCO_3 and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate.

- 5 Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as an oil (2.86 g, 93%).

Part C: To a solution of the protected hydroxamate of part B (2.86 g, 5.27 mmol) in methanol
10 (40 mL) was added acetyl chloride (1.13 mL, 15.8 mmol) and the solution was stirred for 3 hours. The solution was concentrated in vacuo. Reverse phase chromatography (on silica, acetonitrile/ $\text{H}_2\text{O}(\text{HCl})$) provided the title compound as a white solid (2.2 g,
15 84%). MS(CI) MH^+ calculated for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_7\text{S}$: 459, found 459.

Example 11: Preparation of Tetrahydro-N-hydroxy-4-
[[4-(4-phenyl-1-piperidiny)phenyl]
20 sulfonyl]-2H-pyran-4-carboxamide,
monohydrochloride



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Part A: To a solution of Na (8.97 g, 390 mmol) in methanol (1L) at zero degrees Celsius were added 4-fluorothiophenol (50 g, 390 mmol) and methyl chloroacetate (34.2 mL, 390 mmol), and the solution
5 was stirred for 4 hours at ambient temperature. The solution was filtered to remove salts and the filtrate was concentrated in vacuo to provide the sulfide as a colorless oil (75.85 g, 97%).

Part B: To a solution of the sulfide of
10 part A (75.85 g, 380 mmol) in methanol (1L) and H₂O (100 mL) was added Oxone® (720 g, 1.17 mol) and the solution was stirred for 2 hours. The reaction mixture was filtered to remove the excess salts and the filtrate was concentrated in vacuo. The residue
15 was dissolved into ethyl acetate and washed with H₂O, saturated NaHCO₃ and saturated NaCl, and then dried over magnesium sulfate. Concentration in vacuo provide the sulfone as white solid (82.74 g, 94%)

Part C: To a solution of the sulfone of
20 part B (28.5 g, 123 mmol) in N,N-dimethylacetamide (200 mL) were added potassium carbonate (37.3 g, 270 mmol), bis-(2-bromoethyl)ether (19.3 mL, 147 mmol), 4-dimethylaminopyridine (750 mg, 6 mmol) and tetrabutylammonium bromide (1.98 g, 6 mmol), and the
25 solution was stirred at ambient temperature for 72 hours. The solution was poured into 1N HCl (300 mL) and the resulting precipitate was collected by vacuum filtration. Recrystallization (ethyl acetate/hexane) provided the tetrahydropyran compound as a beige
30 solid (28.74 g, 77%).

Part D: To a solution of the tetrahydropyran compound of part C (1.21 g, 4.0 mmol) in DMSO (10 mL) were added Cs_2CO_3 (3.26 g, 10.0 mmol) and 4-phenylpiperidine (640 mg, 4.0 mmol), and the solution was heated to 90 degrees Celsius for 2 hours. The solution was diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with 5 percent aqueous KHSO_4 , saturated NaHCO_3 , and saturated NaCl and dried over magnesium sulfate. Concentration in vacuo provided the amine as a white solid (1.2 g, 67%).

Part E: To a solution of the amine of part D (815 mg, 1.84 mmol) in methanol (5 mL) and THF (5 mL) was added 50 percent aqueous NaOH (2 mL) and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated in vacuo and the residue was diluted with H_2O and acidified to a pH value of 7. The resulting precipitate was collected by vacuum filtration to provide the acid as a white solid (680 mg, 86%).

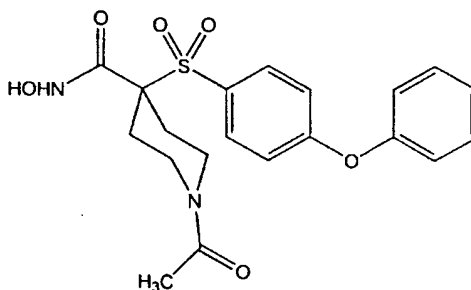
Part F: To a solution of the acid of part E (620 mg, 1.44 mmol) in dichloromethane (10 mL) and DMF (3 mL) were added PyBroP (810 mg, 1.73 mmol), N-methylmorpholine (0.5 mL, 4.3 mmol) and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (190 mg, 1.59 mmol) and the solution was stirred for 4 hours at ambient temperature. The solution was concentrated in vacuo, the residue dissolved into ethyl acetate and washed with H_2O and saturated NaCl , and then dried over Na_2SO_4 . Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as

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a white solid (630 mg, 83%). MS(CI) MH⁺ calculated for C₂₈H₃₆N₂O₆S: 529, found 529.

Part G: To a solution of the protected hydroxamate of part F (600 mg, 1.14 mmol) in dioxane (1.5 mL) and methanol (1.5 mL) was added 4N HCl in dioxane (1.5 mL), and the solution was stirred for 2 hours. The solution was poured into ethyl ether and the resulting precipitate was collected by vacuum filtration to provide the title compound as a beige solid (500 mg, 91%). MS(CI) M+Li⁺ calculated for C₂₃H₂₈N₂O₅S: 445, found 445.

Example 12: Preparation of 1-acetyl-N-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-4-piperidinecarboxamide



Part A: To a solution of the sulfone of Example 6, part D (2.75 g, 5.6 mmol) in THF (10 mL) and ethanol (10 mL) was added NaOH (2.25 g, 56 mmol), and the solution was heated to 70 degrees Celsius for 18 hours. The solution was concentrated in vacuo, the residue was dissolved into H₂O and extracted with ethyl ether. The aqueous solution was acidified to a pH value of 2 and extracted with ethyl acetate. The

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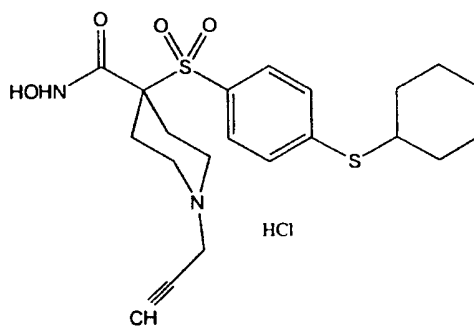
organic layer was dried over magnesium sulfate. Concentration in vacuo provided the crude acid as a solid. A solution of the acid in dichloromethane (6 mL) and trifluoroacetic acid (6 mL) was stirred for 1
5 hour at ambient temperature. Concentration in vacuo provided the amine hydrochloride salt as a solid (2.3 g, quantitative yield).

Part B: To a solution of the amine hydrochloride salt of part A (2.3 g, < 5.6 mmol) in
10 acetone (10 mL) and H₂O (10 mL) cooled to zero degrees Celsius were added triethylamine (1.17 mL, 8.4 mmol) and acetyl chloride (0.60 mL, 8.4 mmol), and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo to
15 remove the acetone and the aqueous solution was extracted with ethyl ether. The aqueous layer was acidified to a pH value of 2 and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentration in vacuo provided the N-
20 acetyl compound as a white solid (1.5 g, 65.2%).

Part C: To a solution of the N-acetyl compound of part B (0.6 g, 1.49 mmol) in DMF (10 mL) were added EDC (401 mg, 2.1 mmol) followed by 50 percent aqueous hydroxylamine (0.9 mL) and 4-
25 methyldmorpholine (0.7 mL, 6.4 mmol), and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated in vacuo and the residue was dissolved into ethyl acetate. The organic layer was washed with H₂O and dried over magnesium sulfate.
30 Reverse phase chromatography (on silica, acetonitrile/H₂O) provided the title compound as a

white solid (101 mg, 16%). MS(CI) MH^+ calculated for $C_{20}H_{22}N_2O_6S$: 419, found 419.

5 Example 13: Preparation of 4-[[4-(cyclohexylthio)-phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the propargyl amine of Example 9, part F (6.5 g, 18.4 mmol) in DMF (10 mL) were added potassium carbonate (3.81 g, 27.6 mmol) and cyclohexyl mercaptan (3.37 mL, 27.6 mmol). The solution was heated to 100 degrees Celsius for 6.5 hours. The solution was diluted with H_2O and extracted with ethyl acetate. The organic layers were dried over magnesium sulfate. Chromatography (on silica, hexane/ethyl acetate) provided the sulfide as a yellow oil (6.05 g, 73%).

Part B: To a solution of the sulfide of part B (612 mg, 1.4 mmol) in ethanol (8.4 mL) and H_2O (1.4 mL) was added potassium hydroxide (470 mg, 8.4 mmol), and the solution was refluxed for 3 hours.

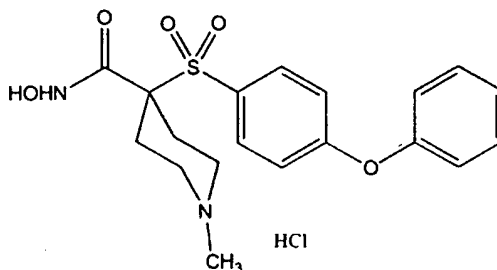
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The solution acidified to a pH value of 3 and was concentrated in vacuo. The residue was dissolved into acetonitrile (10 mL) and to this solution were added O-tetrahydro-2H-pyran-2-yl-hydroxylamine (230 mg, 2.0 mmol) and triethylamine (0.5 mL) followed by EDC (380 mg, 2.0 mmol), and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and the residue was diluted with saturated NaHCO₃ and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as an oil (246 mg, 34%).

Part C: To a solution of the protected hydroxamate of part B (246 mg, 0.47 mmol) in methanol (4 mL) was added acetyl chloride (0.11 mL, 1.5 mmol), and the solution was stirred at ambient temperature for 3 hours. After concentration in vacuo, reverse phase chromatography (on silica, acetonitrile/H₂O(HCl)) provided the title compound as a white solid (223 mg, quantitative yield).

Example 14: Preparation of N-hydroxy-1-methyl-4-
[(phenoxyphenyl)sulfonyl]-4-
piperidinecarboxamide, monohydrochloride

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Part A: To a solution of the sulfone of Example 6, part D (2.67 g, 5.5 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (5 mL), and the solution was stirred at ambient temperature for 2 hours. The solution was concentrated in vacuo and the residue was triturated with ethyl ether to provide the crude amine trifluoroacetic acid salt. To a solution of the crude amine salt in methanol (10 mL) were added formaldehyde (37 percent aqueous solution, 2.0 mL, 27.5 mmol) and borane pyridine (2.2 mL, 22 mmol), and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo. The residue was dissolved into ethyl acetate, washed with H₂O and dried over magnesium sulfate. Concentration in vacuo provided the N-methyl compound as a yellow oil (2.17 g, 98%).

Part B: To a solution of the N-methyl compound of part A (2.17 g, 5.4 mmol) in ethanol (10 mL) and THF (10 mL) was added NaOH (2.0 g, 50 mmol), and the reaction mixture was stirred at minus 65 degrees Celsius for 18 hours. The solution was concentrated in vacuo. The residue was dissolved into H₂O and extracted with ethyl ether. The aqueous

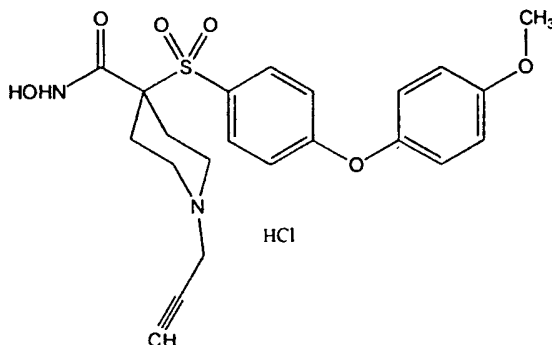
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solution was acidified to a pH value of 2 and the resulting solid was collected by vacuum filtration to provide the acid as a white solid (1.8 g, 90%).

Part C: To a solution of the acid of part
5 B (0.5 g, 1.3 mmol) in DMF (10 mL) were added EDC
(1.06 g, 5.5 mmol) followed by O-tetrahydro-2H-pyran-
2-yl-hydroxylamine (490 mg, 4.2 mmol) and 4-
methymorpholine (0.76 mL) and the solution was
stirred at ambient temperature for 18 hours. The
10 solution was concentrated in vacuo and the residue
was dissolved into ethyl acetate, washed with H₂O and
dried over magnesium sulfate. Concentration in vacuo
provided the crude protected hydroxamate. To a
solution of the crude hydroxamate in methanol (10 mL)
15 was added acetyl chloride (0.28 mL, 3.9 mmol), and
the solution was stirred for 3 hours at ambient
temperature. The solution was concentrated in vacuo.
Reverse phase chromatography (on silica,
acetonitrile/H₂O(0.0125% HCl) provided the title
20 compound as a white solid (261 mg, 46%). MS(CI) MH⁺
calculated for C₁₉H₂₂N₂O₅S: 391, found 391.

Example 15: Preparation of N-hydroxy-4-[[4-(4-
methoxyphenoxy)phenyl]sulfonyl]-1-(2-
25 propynyl)-4-piperidinecarboxamide,
monohydrochloride

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Part A: To a solution of the propargyl
amine of Example 9, part F (2.00 g, 5.66 mmol) in DMF
5 (10 mL) were added cesium carbonate (4.7 g, 14.5
mmol) and 4-methoxythiophenol (1.80 g, 14.5 mmol),
and the solution was heated to 95 degrees Celsius for
24 hours. The solution was diluted with ethyl
acetate and washed with 1N NaOH and saturated NaCl,
10 and then dried over magnesium sulfate.
Chromatography (on silica, ethyl acetate/hexane)
provided the phenoxy compound as a solid (2.67 g,
quantitative yield).

Part B: To a solution of the phenoxy
15 compound of part A (2.40 g, 5.25 mmol) in ethanol (30
mL) and H₂O (6 mL) was added potassium hydroxide (2.0
g, 31.37 mmol), and the solution was heated to reflux
for 4 hours. The solution was acidified with
concentrated HCl to a pH value of 3 and the residue
20 was collected by vacuum filtration to provide the
crude acid that was carried on without additional
purification.

Part C: To a solution of the acid of part
B (2.25 g, 5.25 mmol) in acetonitrile (30 mL) were
25 added triethylamine (1 mL) and O-tetrahydro-2H-pyran-

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2-yl-hydroxylamine (1.34 g, 9.0 mmol). After the solution was stirred for 15 minutes, EDC (1.72 g, 9.0 mmol) was added the solution was stirred at ambient temperature for 18 hours. The solution was
5 concentrated in vacuo and the residue was dissolved into ethyl acetate. The ethyl acetate solution was washed with saturated NaHCO_3 , H_2O and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the protected
10 hydroxamate as a white solid (0.93 g, 33%).

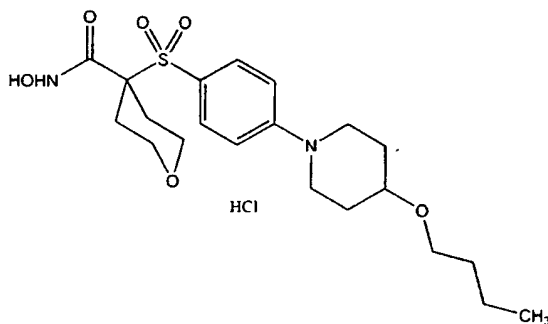
Part D: To a solution of the protected hydroxamate of part C (0.93 g, 1.7 mmol) in methanol (15 mL) was added acetyl chloride (0.36 mL, 5.1 mmol) and the solution was stirred for 3 hours. The
15 solution was concentrated in vacuo to provide the title compound as a white solid (650 mg, 82%).
Analytical calculation for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_6\text{S HCl}$: C, 54.84; H, 5.24; N, 5.82; S, 6.67; Cl, 6.67. Found: C, 53.10; H, 5.07; N, 5.59; S, 7.04; Cl, 6.32.

20

Example 16: Preparation of 4-[[4-(4-butoxy-1-piperidinyl)phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide,
monohydrochloride

25

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Part A: To a solution of the tetrahydropyran compound of Example 11, part C (1.95 g, 6.46 mmol) in DMSO (25 mL) were added Cs₂CO₃ (7.4 g, 22.6 mmol) and 4-butoxypiperidine (1.25 g, 6.46 mmol) and the solution was heated to 90 degrees Celsius for 1 hour. The solution was quenched with H₂O and extracted with ethyl acetate. The organic layer was washed with 5 percent aqueous KHSO₄, saturated NaHCO₃, and saturated NaCl, and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/dichloromethane) provided the amine as a yellow oil (1.85 g, 65%).

Part B: To a solution of the amine of part A (1.65 g, 3.76 mmol) in THF (10 mL) was added potassium trimethylsilanolate (530 mg, 4.13 mmol), and the solution was stirred for 22 hours at ambient temperature. The solution was concentrated in vacuo and the crude residue was used as is in the next reaction.

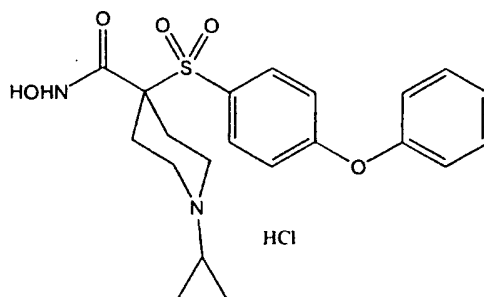
Part C: To a solution of the crude acid of part B (1.74 g, 3.76 mmol) in dichloromethane (10 mL) were added PyBroP (2.10 g, 4.51 mmol), N-methylmorpholine (1.24 mL, 11.3 mmol) and O-

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tetrahydro-2H-pyran-2-yl-hydroxylamine (484 mg, 4.14 mmol), and the solution was stirred for 30 minutes at ambient temperature. The solution was concentrated in vacuo. The residue was dissolved into ethyl acetate and washed with H₂O and saturated NaCl, and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane/methanol) provided the protected hydroxamate as a colorless oil (1.5 g, 76% over two steps).

Part D: To a solution of the protected hydroxamate of part C (1.25 g, 2.4 mmol) in dioxane (3 mL) was added 4N HCl in dioxane (3 mL), and the solution was stirred for 15 minutes. After methanol (3 mL) was added the solution was stirred for 5 hours at ambient temperature. The solution was poured into ethyl ether and the resulting precipitate was collected by vacuum filtration to provide the title compound as a white solid (1.0 g, 88%). MS(CI) MH⁺ calculated for C₂₁H₃₂N₂O₆S: 441, found 441.

Example 17: Preparation of 1-cyclopropyl-N-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-4-piperidinecarboxamide, monohydrochloride



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Part A: To a solution of the amine hydrochloride salt of Example 6, part E (2.13 g, 5.0 mmol) in methanol (25 mL) was added 3A molecular sieves, acetic acid (2.86 mL, 50 mmol) and the solution was stirred for 5 minutes. To this solution was added ((1-ethoxycyclopropyl)oxy)-trimethylsilane (6.08 mL, 30 mmol) followed by sodium cyanoborohydride (1.41 g, 22.0 mmol), and the solution was heated to reflux for 18 hours. The excess salts and sieves were collected by filtration and the filtrate was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with 1N NaOH, H₂O and saturated NaCl, and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the cyclopropyl amine as a white solid (1.90 g, 86%).

Part B: To a solution of the cyclopropyl amine of part A (1.9 g, 4.2 mmol) in THF (12 mL) and ethanol (12 mL) was added NaOH (1.71 g, 4.3 mmol) in H₂O (10 mL), and the solution was heated to 62 degrees Celsius for 20 hours. The solution was concentrated in vacuo and the residue was diluted with H₂O and acidified to a pH value of 5 with 1N HCl. The resulting solid was collected by vacuum filtration to provide the acid as a white solid (1.49 g, 82%). MS(CI) MH⁺ calculated for C₂₁H₂₃NO₅S: 402, found 402. HRMS calculated for C₂₁H₂₃NO₅S: 402.1375, found 402.1350.

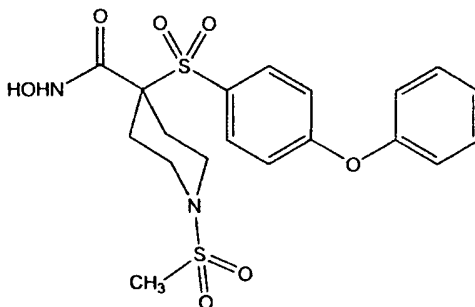
Part C: To a solution of the acid of part C (1.49 g, 3.4 mmol) in dichloromethane (50 mL) was added triethylamine (1.42 mL, 10.21 mmol) followed by

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50 percent aqueous hydroxylamine (2.25 mL, 34.0 mmol) and PyBroP (3.17 g, 6.8 mmol), and the solution was stirred for 72 hours. The mixture was diluted with H₂O and the organic layer was separated, washed with saturated NaCl and dried over magnesium sulfate. Concentration in vacuo followed by reverse phase chromatography (on silica, acetonitrile/H₂O) provided the hydroxamate.

The hydrochloride salt was prepared by dissolving the free base (830 mg, 2.0 mmol) in methanol (20 mL) followed by the addition of acetyl chloride (0.17 mL, 2.0 mmol). The solution was stirred for 10 minutes at zero degrees Celsius. The resulting white solid was collected by vacuum filtration and washed with cold ethyl ether to provide the title compound (595 mg, 66%). HRMS calculated for C₂₁H₂₄N₂O₅S: 416.1407, found 416.1398. Analytical calculation for C₂₁H₂₄N₂O₅S: C, 55.68; H, 5.56; N, 6.18; S, 7.08; Cl, 7.83. Found: C, 55.39; H, 5.72; N, 6.15; S, 7.29; Cl, 8.17.

Example 18: Preparation of N-hydroxy-1-(methanesulfonyl)-4-(phenoxyphenyl)-sulfonyl-1-piperidinecarboxamide



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Part A: To a solution of the amine hydrochloride salt of Example 6, part E (1.06 g, 2.5 mmol) in dichloromethane (10 mL) were added
5 triethylamine (0.76 mL, 5.5 mmol) and methanesulfonyl chloride (0.23 mL, 3.0 mmol), and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate and H₂O. The
10 organic layer was washed with H₂O and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the methanesulfonamide as a solid (2.1 g, 58%).

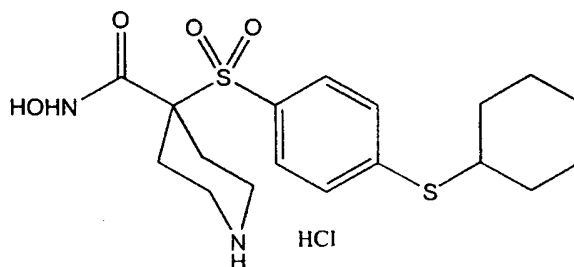
Part B: To a solution of the
15 methanesulfonamide of part A (2.0 g, 4.15 mmol) in ethanol (12 mL) and H₂O (12 mL) was added NaOH (1.66 g, 41.5 mmol), and the solution was heated to 65 degrees Celsius for 18 hours. The solution was concentrated in vacuo and the remaining aqueous
20 solution was acidified to a pH of 4. The solution was extracted with ethyl acetate and the organic layer was washed with saturated NaCl and dried over magnesium sulfate. Concentration in vacuo provided the acid as a yellow foam (1.46 g, 80%).

25 Part C: To a solution of the acid of part B (1.46 g, 3.38 mmol) in dichloromethane (50 mL) were added triethylamine (1.41 mL, 10.1 mmol), 50 percent aqueous hydroxylamine (2.2 mL, 33.8 mmol) and PyBroP (3.16 g, 6.76 mmol), and the solution was stirred at
30 ambient temperature for 72 hours. The solution was diluted with H₂O and the organic layer was separated

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and washed with saturated NaCl, and then dried over magnesium sulfate. Reverse phase chromatography (on silica, acetonitrile/H₂O) followed by trituration with ethyl ether provide the title compound as a white solid (160 mg, 11%). Analytical calculation for C₁₉H₂₂N₂O₇S₂: C, 50.21; H, 4.88; N, 6.16; S, 14.11. Found: C, 48.72; H, 5.36; N, 5.61; S, 12.81.

10 Example 19: Preparation of 4-[[4-(cyclohexylthio)-phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride



15

Part A: To a solution of the sulfone of Example 9, part D (10.1 g, 24.0 mmol) in DMF (20 mL) were added K₂CO₃ (5.0 g, 36.0 mmol) and cyclohexylmercaptan (4.4 mL, 36.0 mmol), and the solution was heated at 85 degrees Celsius for 6.5 hours. The solution was partitioned between ethyl acetate and H₂O. The organic layer was washed with saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as a oil (8.2 g, 67%).

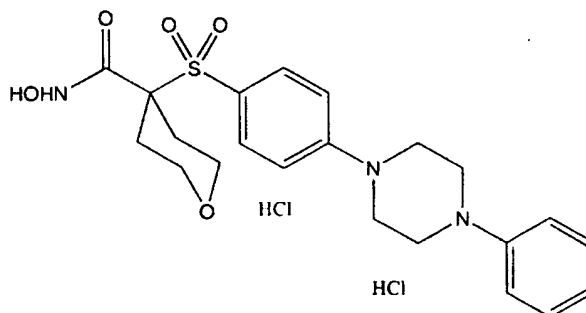
-333-

Part B: To a solution of the sulfide (2.32 g, 4.5 mmol) in ethanol (10 mL) and THF (10 mL) was added NaOH (1.81 g, 45 mmol) in H₂O (10 mL), and the solution was heated to 65 degrees Celsius for 18
5 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to a pH value of 2. The solution was extracted with dichloromethane and dried over magnesium sulfate. Concentration in vacuo provided the acid as a white solid (830 mg, 38%).

10 Part C: To a solution of the acid of part B (2.0 g, 4.0 mmol) in dichloromethane (25 mL) were added N-methylmorpholine (1.32 mL, 12.0 mmol), PyBrop (2.12 g, 2.12 mmol) and 50 percent aqueous hydroxylamine (2.6 mL, 40 mmol), and the solution was
15 stirred for 18 hours at ambient temperature. The solution was diluted with H₂O and the layers were separated. The organic layer was washed with saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/methanol)
20 provided the hydroxamate as a white solid (1.4 g, 70%).

Part D: Into a solution of the hydroxamate of part C (1.31 g, 2.63 mmol) in ethyl acetate (70 mL) cooled to zero degrees Celsius was bubbled HCl
25 gas for 30 minutes. The solution was concentrated in vacuo. Reverse phase chromatography (on silica, acetonitrile/H₂O(HCl)) provided the title compound as a white solid (378 mg, 33%). Analytical calculation for C₁₈H₂₆N₂O₄S₂: C, 49.70; H, 6.26; N, 6.44; S, 14.74;
30 Cl, 8.15. Found: C, 48.99; H, 6.34; N, 6.24; S, 14.66; Cl, 8.56.

Example 20: Preparation of tetrahydro-N-hydroxy-4-
[[4-(4-phenyl-1-piperazinyl)phenyl]
sulfonyl]-2H-pyran-4-carboxamide,
5 dihydrochloride



Part A: To a solution of the
10 tetrahydropyran compound of Example 11, part C (1.96
g, 6.5 mmol) in DMSO (20 mL) were added Cs₂CO₃ (4.9 g,
15 mmol) and 4-phenylpiperazine (1.1 mL, 7.15 mmol),
and the solution was heated to 90 degrees Celsius for
45 minutes. The solution was quenched by the
15 addition of H₂O and was extracted with ethyl acetate.
The organic layer was washed with 5 percent aqueous
KHSO₄, saturated NaHCO₃, and saturated NaCl and dried
over magnesium sulfate. Concentration in vacuo
provided the amine as a beige solid (1.7 g, 59%).

20 Part B: To a solution of the amine of part
A (1.5 g, 3.38 mmol) in THF (20 mL) was added
potassium trimethylsilanolate (480 mg, 3.72 mmol),
and the solution was stirred at ambient temperature
for 22 hours. Concentration in vacuo provided the

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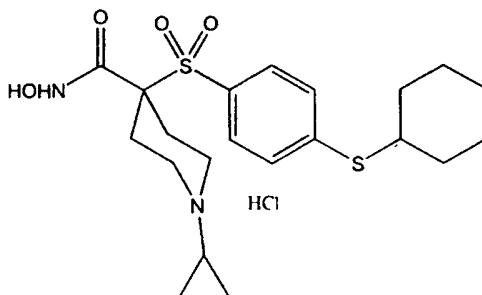
crude acid salt to be used without purification in the next step.

Part C: To a solution of the acid salt of part B (1.58 g, 3.38 mmol) in dichloromethane (10 mL) and DMF (3 mL) were added PyBroP (1.89 g, 4.06 mmol), N-methylmorpholine (1.1 mL, 10.1 mmol) and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (435 mg, 3.72 mmol), and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate and H₂O and the organic layer was washed with H₂O and saturated NaCl, and then dried over magnesium sulfate. Chromatography (on silica, dichloromethane/methanol) provided the protected hydroxamate as a white foam (1.7 g, 95% over two steps).

Part D: To a solution of the protected hydroxamate of part C (1.28 g, 2.4 mmol) in dioxane (5 mL) and methanol (5 mL) was added 4N HCl in dioxane (5 mL), and the solution was stirred for 2 hours at ambient temperature. The solution was poured into ethyl ether and the resulting precipitate was collected by vacuum filtration to provide the title compound as a white solid (900 mg, 73%). MS(CI) MH⁺ calculated for C₂₂H₂₇N₃O₅S: 446, found 446.

Example 21: Preparation of 4-[[4-(cyclohexylthio)-phenyl]sulfonyl]-1-cyclopropyl)-N-hydroxy-4-piperidine carboxamide, monohydrochloride

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Part A: To a solution of the sulfone of Example 9, part D (10.1 g, 24.0 mmol) in DMF (20 mL) were added K₂CO₃ (5.0 g, 36.0 mmol) and cyclohexylmercaptan (4.4 mL, 36.0 mmol), and the solution was heated at 85 degrees Celsius for 6.5 hours. The solution was partitioned between ethyl acetate and H₂O. The organic layer was washed with saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as a oil (8.2 g, 67%).

Part B: HCl gas was bubbled for 30 minutes into a solution of the sulfide of part B (8.2 g, 17.0 mmol) in ethyl acetate (100 mL) cooled to zero degrees Celsius. The solution was concentrated in vacuo to provide the amine as a white solid (5.99 g, 79%). MS(CI) MH⁺ calculated for C₂₀H₂₉NO₄S: 412, found 412.

Part C: To a solution of the amine of part B (2.24 g, 5.0 mmol) in methanol (20 mL) was added acetic acid (2.86 mL, 50 mmol) followed by (1-ethoxycyclopropyl) oxytrimethylsilane (6.03 mL, 30 mmol) and sodium borohydride (1.41 g, 22.5 mmol), and the solution was refluxed for 18 hours. The solution

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was concentrated in vacuo and the residue was dissolved into ethyl acetate and washed with 1N NaOH, H₂O and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the cyclopropyl amine as a white solid (1.97 g, 87%).

Part D: To a solution of the cyclopropyl amine of part C (1.9 g, 4.2 mmol) in ethanol (10 mL) and THF (10 mL) was added NaOH (1.68 g, 42.0 mmol) in H₂O (10 mL) and the solution was heated at sixty-eight degrees Celsius for 18 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to a pH value of 2. The resulting solid was collected and washed with ethyl ether to provide the acid as a white solid (1.61 g, 81%). HRMS calculated for C₂₁H₂₉NO₄S₂: 424.1616, found 424.1615.

Part E: To a solution of the acid of part D (1.61 g, 3.0 mmol) in dichloromethane (30 mL) were added N-methylmorpholine (1.0 g, 9.0 mmol), PyBrop (1.54 g, 3.3 mmol) and 50 percent aqueous hydroxylamine (2.0 mL, 30 mmol), and the solution was stirred for 18 hours at ambient temperature. The residue was concentrated in vacuo. The residue was partitioned between ethyl acetate and H₂O, the organic layer washed with H₂O and saturated NaCl, and then dried over magnesium sulfate. Filtration through a silica pad (ethyl acetate/methanol) gave the hydroxamate as a white solid (1.07 g, 80%).

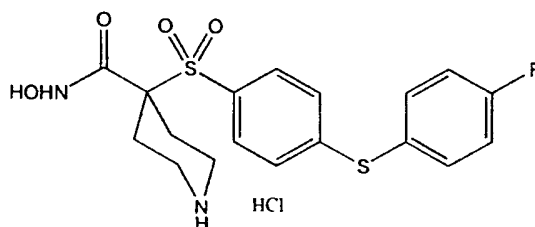
Part F: To a solution of the hydroxamate of part F (1.07 g, 2.4 mmol) in cold methanol (2 mL) was added acetyl chloride (0.27 mL, 3.6 mmol), and

the solution was stirred for 30 minutes. The solution was concentrated in vacuo. Reverse phase chromatography (acetonitrile/H₂O(HCl)) provided the title compound as a white solid (245 mg, 21%).

5

Example 22: Preparation of 4-[[4-[(4-fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide, monohydrochloride

10



Part A: To a solution of the sulfone of Example 9, part D (6.0 g, 14.4 mmol) in DMF (30 mL) were added potassium carbonate (2.39 mg, 17.3 mmol) and 4-fluorothiophenol (3.0 mL, 28.1 mmol), and the solution was stirred at ambient temperature for 18 hours. The solution was diluted with ethyl acetate and washed with 1N NaOH and saturated NaCl, and then dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as a solid (6.6 g, 87%).

Part B: To a solution of the sulfide of part A (6.6 g, 12.6 mmol) in ethanol (90 mL) and H₂O (20 mL) was added sodium hydroxide (5.04 g, 126 mmol), and the solution was heated at 70 degrees Celsius for 18 hours. The mixture was acidified to a

-339-

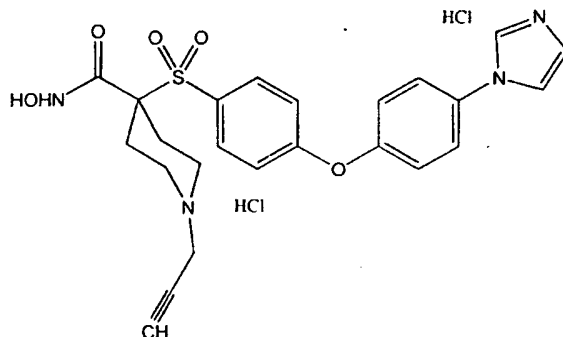
pH value of 4 and the solution was extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/ethanol) provided the solid acid (4.8 g, 79%).

Part C: To a solution of the acid of part B (4.8 g, 10.0 mmol) in DMF (30 mL) was added 4-methylmorpholine (3.03 g, 30.0 mmol) followed by O-tetrahydro-2H-pyran-2-yl-hydroxylamine (7.45 g, 50.0 mmol) and PyBroP (5.59 g, 12.0 mmol), and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated in vacuo. The residue was dissolved into ethyl acetate and washed with H₂O and saturated NaCl, and then dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a white solid (4.0 g, 67%).

Part D: HCl gas was bubbled for 5 minutes into a solution of the protected hydroxamate of part D (4.0 g, 6.7 mmol) in ethyl acetate (120 mL) followed by stirring at ambient temperature for 1.5 hours. The resulting solid was collected by vacuum filtration to provide the title compound as a white solid (1.90 g, 64%). MS(CI) MH⁺ calculated for C₁₈H₁₉N₂O₄S₂F: 411, found 411.

Example 23: Preparation of N-hydroxy-4-[[4-[4-(1H-imidazol-1-yl)phenoxy] phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, dihydrochloride

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Part A: To a solution of the amine hydrochloride salt of Example 9, part F (3.00 g, 8.49 mmol) in DMF (13 mL) were added K_2CO_3 (2.35 g, 17.0 mmol) and 4-(imidazol-1-yl)phenol (2.72 g, 17.0 mmol), and the solution was heated to 85 degrees Celsius for 64 hours. The solution was concentrated and the residue was partitioned between ethyl acetate and H_2O . The organic layer was washed with H_2O and saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, chloroform/methanol) provided the ethyl ester as a white foam (2.36 g, 56%).

Part B: To a solution of the ethyl ester of part A (2.36 g, 5.33 mmol) in ethanol (2.8 mL) and H_2O (4.6 mL) was added KOH (1.80 g, 32.1 mmol), and the solution was heated to 100 degrees Celsius for 4.5 hours. The solution was acidified to a pH value of 1 with concentrated HCl solution and then concentrated to provide the acid as a tan solid that was used without additional purification (2.87 g).

Part C: To a solution of the acid of part B (2.87 g, 5.33 mmol) in acetonitrile (24 mL) were added O-tetrahydro-2H-pyran-2-yl-hydroxylamine (870

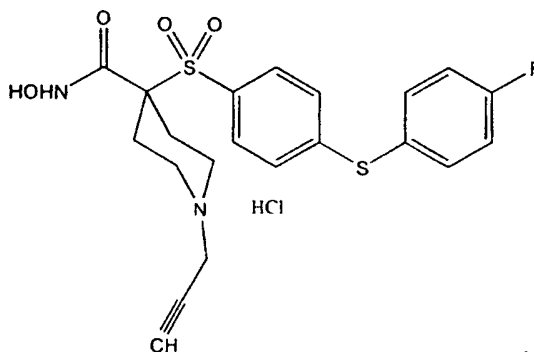
-341-

mg, 7.45 mmol), EDC (1.43 g, 7.45 mmol) and N-methylmorpholine (1.21 mL, 11.0 mmol) and the solution was stirred for 18 hours at ambient temperature. The solution was concentrated and the residue was diluted with H₂O and extracted with ethyl acetate. The organic layer was washed with H₂O and saturated NaCl and dried over magnesium sulfate. Chromatography (chloroform, methanol) provided the protected hydroxylamine as a white solid (1.62 g, 53%).

Part D: To a solution of the protected hydroxylamine of part C (1.60 g, 2.83 mmol) in methanol (23 mL) was added acetyl chloride (0.61 mL, 8.52 mmol), and the solution was stirred for 1 hour. The solution was concentrated in vacuo. Reverse phase chromatography (on silica, acetonitrile/H₂O) provided the title compound as a white solid (975 mg, 62%). MS(CI) MH⁺ calculated for C₂₄H₂₅N₄O₅S: 481, found 481. Analytical calculation for C₂₄H₂₅N₄O₅S 2HCl: C, 52.08; H, 4.73; N, 10.12; S, 5.79; Cl, 12.81. Found: C, 51.59; H, 4.84; N, 10.93; S, 5.51; Cl, 11.98.

Example 24: Preparation of 4-[[4-[(4-fluorophenyl)thiophenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride

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Part A: To a solution of the propargyl amine of Example 9, part F (4.06 g, 11.49 mmol) in DMF (20 mL) were added potassium carbonate (3.18 g, 22.98 mmol) and 4-fluorothiophenol (2.95 g, 22.98 mmol), and the solution was stirred for 18 hours at ambient temperature. The solution was diluted with ethyl acetate, washed with 1N NaOH and saturated NaCl, and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as a solid (4.46 g, 84%).

Part B: To a solution of the sulfide of part A (4.46 g, 9.7 mmol) in tetrahydropyran (90 mL), H₂O (30 mL) and ethanol (30 mL) was added NaOH (3.86 g, 97.0 mmol), and the solution was heated to 65 degrees Celsius for 2 hours. The solution was concentrated in vacuo and the residue was dissolved into H₂O and acidified to a pH value of 4 with 2N HCl. The resulting residue was collected by vacuum filtration to provide the acid as a white solid (4.0 g, 95%).

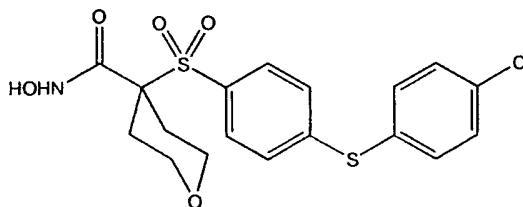
Part C: To a solution of the acid of part B (4.0 g, 9.2 mmol) in DMF (50 mL) and 4-methylmorpholine (2.8 g, 27.7 mmol) was added O-

-343-

tetrahydro-2H-pyran-2-yl-hydroxylamine (6.88 g, 46.1 mmol) and PyBroP (5.16 g, 11.1 mmol), and the solution was stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and the residue was dissolved into ethyl acetate. The solution was washed with H₂O and saturated NaCl, and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the protected hydroxamate as a white solid (2.8 g, 56%).

10 Part D: HCl gas was bubbled for 10 minutes into a solution of the protected amine of part C (2.8 g, 5.1 mmol) in ethyl acetate (100 mL), and the solution was then stirred for 1 hour. The solution was concentrated in vacuo and the solid
15 recrystallized (ethanol) to provide the title compound as a white solid (1.12 g, 45%). MS(CI) MH⁺ calculated for C₂₁H₂₁N₂O₄S₂F: 449, found 449.

20 Example 25: Preparation of 4-[[4-[(4-chlorophenyl)-thio]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



25 Part A: To a solution of the tetrahydropyran compound of Example 11, part C (8.0 g, 26.5 mmol) in THF (250 mL) was added potassium

-344-

trimethylsilonate (10.2 g, 79.5 mmol), and the solution was stirred for 1.5 hours. The reaction was quenched by the addition of H₂O, acidified to a pH value of 2.5, and the solution was extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na₂SO₄. Concentration in vacuo provide the acid salt as a white solid (5.78 g, 76%).

Part B: To a solution of the acid salt of part A (5.4 g, 18.7 mmol) in DMF (35 mL) were added HOBT (3.04 g, 22.5 mmol), N-methylmorpholine (6.2 mL, 56.2 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (6.8 g, 58.1 mmol) and EDC (5.0 g, 26.2 mmol), and the solution was stirred for 3 hours at ambient temperature. The solution was concentrated in vacuo, the residue partitioned between ethyl acetate and H₂O, and the organic layer was washed with 5 percent aqueous KHSO₄, H₂O, saturated NaHCO₃ and saturated NaCl, and then dried over Na₂SO₄. Concentration in vacuo provided the protected hydroxamate as a white solid (6.34 g, 87%).

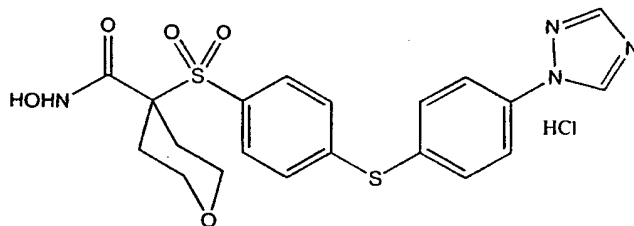
Part C: To a solution of p-chlorothiophenol (2.71 g, 18.7 mmol) in DMF (10 mL) was added K₂CO₃ (2.6 g, 18.7 mmol) followed by the protected hydroxamate of part B (2.9 g, 7.5 mmol) and the solution was heated at 75 degrees Celsius for 5 hours. The solution was concentrated in vacuo, the residue partitioned between ethyl acetate and H₂O, the organic layer was washed with saturated NaCl, and dried over Na₂SO₄. Chromatography (on silica, ethyl acetate/hexane/methanol) provided the sulfide as a

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white foam (3.56 g, 93%). MS(CI) MH^+ calculated for $C_{23}H_{26}ClNO_6S_2$: 512, found 512.

Part D: To a solution of the sulfide of part C (3.5 g, 6.8 mmol) in dioxane (10 mL) was added
5 4N HCl in dioxane (10 mL). After 10 minutes of stirring, methanol (10 mL) was added with continued stirring for one hour. The solution was concentrated in vacuo. Recrystallization (acetone/hexane) provided the title compound as a white solid (2.4 g,
10 83%). MS(CI) MH^+ calculated for $C_{18}H_{18}ClNO_5S$: 428, found 428.

Example 26: Preparation of Tetrahydro-N-hydroxy-4-[[4-[4-(1H-1,2,4-triazol-1-yl)phenoxy]-phenyl]-sulfonyl]-2H-pyran-4-,
15 carboxamide, monohydrochloride



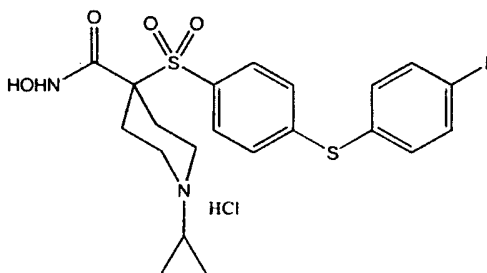
20 Part A: To a solution of the protected hydroxamate of Example 25, part B (2.9 g, 7.5 mmol) in DMF (10 mL) was added 4-(1,2,4-triazol-1-yl)phenol (2.47 g, 15 mmol) in DMF (5 mL) followed by Cs_2CO_3 (7.33 g, 22.5 mmol), and the solution was heated at
25 95 degrees Celsius for 5 hours. The solution was concentrated in vacuo and the residue was partitioned between ethyl acetate and H_2O . The organic layer was

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washed with saturated NaCl and dried over Na₂SO₄.
Chromatography (on silica, ethyl
acetate/hexane/methanol) provided the phenol as a
white solid (3.16 g, 80%).

5 Part B: To a solution of the phenol of
part A (2.8 g, 5.3 mmol) in dioxane (10 mL) was added
4N HCl in dioxane (10 mL). After 5 minutes of
stirring, methanol (10 mL) was added and stirring was
continued for 1 hour. The solution was then poured
10 into ethyl ether, and the resulting precipitate was
collected by vacuum filtration to provide the title
compound as a white solid (2.44 g, 96%). MS(CI) MH⁺
calculated for C₂₀H₂₀N₄O₆S: 445, found 445.

15 Example 27: Preparation of 1-cyclopropyl-4-[[4-[(4-
fluorophenyl)thio] phenyl]sulfonyl]-N-
hydroxy-4-piperidinecarboxamide,
monohydrochloride



20

Part A: HCl gas was bubbled for 7 minutes
into a solution of the sulfide of Example 9, part D
(7.06 g, 13.5 mmol) in ethyl acetate (150 mL), and
25 the solution was stirred for 15 minutes at zero
degrees Celsius. The solution was concentrated in

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vacuo to provide the amine as a white solid (6.43 g, quantitative yield).

Part B: To a solution of the amine of part A (6.4 g, 13.9 mmol) in methanol (65 mL) was added
5 acetic acid (7.96 mL, 139 mmol) and a scoop of 3A molecular sieves. To this mixture was added (1-ethoxycyclopropyl)-oxytrimethylsilane (16.8 mL, 84 mmol) followed by sodium cyanoborohydride (3.9 g, 62 mmol). The solution was heated to reflux for 6
10 hours. The solution was filtered and the filtrate was concentrated in vacuo. The residue was dissolved into ethyl acetate, washed with H₂O, 2N NaOH and saturated NaCl, and dried over magnesium sulfate. Filtration through a pad of silica (hexane/ethyl
15 acetate) provided the cyclopropyl amine as a white solid (6.49 g, quantitative yield).

Part C: To a solution of the cyclopropyl amine of part B (6.4 g, 13.8 mmol) in ethanol (30 mL) and THF (30 mL) was added NaOH (5.5 g, 138 mmol) in
20 H₂O (23 mL), and the solution was heated to 65 degrees Celsius for 12 hours. The solution was concentrated in vacuo and the aqueous layer was acidified to a pH value of 2 with 2N HCl. The resulting white precipitate was collected by filtration to provide
25 the acid as a white solid (5.2 g, 87%). MS(CI) MH⁺ calculated for C₂₁H₂₂NO₄S₂F: 436, found 436.

Part D: To a solution of the acid of part C (2.27 g, 5.2 mmol) in DMF (60 mL) was added HOBT (845 mg, 6.2 mmol) followed by N-methylmorpholine
30 (1.71 mL, 15.6 mmol), EDC (1.40 g, 7.28 mmol) and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (913 mg, 7.8

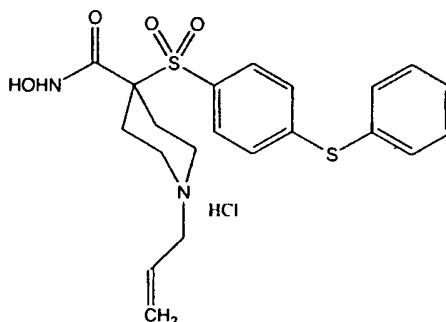
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mmol), and the solution was stirred at ambient temperature for 72 hours. The solution was concentrated in vacuo, the residue was dissolved into dichloromethane and washed with H₂O and saturated NaCl, and then dried over magnesium sulfate. Chromatography (on silica, hexane/ethyl acetate) provided the protected hydroxamate as a white solid (1.95 g, 70%).

Part E: To a solution of the protected hydroxamate of part D (3.2 g, 6.0 mmol) in cold methanol (100 mL) was added acetyl chloride (1.3 mL, 18.0 mmol) in methanol (30 mL), and the solution was stirred at ambient temperature for 4 hours. The solution was concentrated in vacuo and the residue was triturated with ethyl ether to provide the title compound as a white solid (2.86 g, 98%). MS(CI) MH⁺ calculated for C₂₁H₂₃N₂O₄S₂F: 451, found 451. Analytical calculation for C₂₁H₂₃N₂O₄S₂F 0.25H₂O HCl: C, 51.32; H, 5.02; N, 5.70; S, 13.05; Cl, 7.21. Found: C, 50.99; H, 4.91; N, 5.65; S, 13.16; Cl, 7.83.

Example 28: Preparation of N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propenyl)-4-piperidine carboxamide, monohydrochloride

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Part A: To a solution of the amine hydrochloride salt of Example 9, part E (4.78 g, 10.8 mmol) in DMF (25 mL) were added K₂CO₃ (2.98 g, 21.6 mmol) and allyl bromide (0.935 mL, 10.8 mmol), and the solution was stirred for 5 hours at ambient temperature. The solution was partitioned between ethyl acetate and H₂O, and the organic layer was washed with H₂O and saturated NaCl, and dried over magnesium sulfate. Filtration through a pad of silica (hexane/ethyl acetate) provided the allyl amine as an oil (4.80 g, quantitative yield).

Part B: To a solution of the allyl amine of part A (4.8 g, 10.8 mmol) in ethanol (25 mL) and THF (25 mL) was added NaOH (4.3 g, 108 mmol) in H₂O (20 mL), and the solution was heated to 65 degrees Celsius for 18 hours. The solution was concentrated in vacuo and diluted with H₂O. The aqueous solution was acidified to a pH value of 3. The resulting precipitate was collected by vacuum filtration to provide the acid as a beige solid (4.1 g, 84%).

MS(CI) MH⁺ calculated for C₂₁H₂₃NO₄S₂: 418, found 418.

Part C: To a solution of the acid of part B (4.1 g, 9.0 mmol) in DMF (90 mL) was added

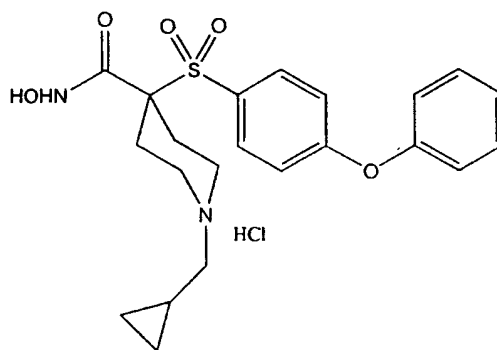
-350-

HOBT(1.46 g, 11.0 mmol) followed by N-methylmorpholine (2.97 mL, 2.7 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.58 g, 13.5 mmol) and EDC (2.42 g, 13.0 mmol), and the solution was stirred
5 for 72 hours. The solution was concentrated in vacuo. The residue was dissolved in dichloromethane and washed with H₂O and saturated NaCl, and then dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/methanol) provided the
10 protected hydroxylamine as a white solid (4.11 g, 88%).

Part D: To a solution of the protected hydroxylamine of part C (4.11 g, 8.0 mmol) in ethyl acetate (100 mL) cooled to zero degrees Celsius was
15 added acetyl chloride (1.71 mL, 24.0 mmol), and the solution was stirred for 4 hours at ambient temperature. The solution was concentrated in vacuo and trituration with ethyl ether provided the title compound as a white solid (3.53 g, 95%). Analytical
20 calculation for C₂₁H₂₄N₂O₄S₂ HCl 0.5H₂O: C, 52.76; H, 5.48; N, 5.86; S, 13.42; Cl, 7.42. Found: C, 52.57; H, 5.69; N, 6.29; S, 12.59; Cl, 7.80.

Example 29: Preparation of 1-(cyclopropylmethyl)-N-
25 hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-4-
piperidine carboxamide, monohydrochloride

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Part A: To a solution of the amine hydrochloride salt of Example 6, part E (2.13 g, 5.0 mmol) in DMF (10 mL) were added K₂CO₃ (1.4 g, 10.0 mmol) and bromomethylcyclopropane (0.48 mL, 5.0 mmol), and the solution was stirred for 18 hours at ambient temperature. The solution was partitioned between ethyl acetate and H₂O, the organic layer was washed with H₂O and saturated NaCl, and then dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the solid cyclopropylmethylamine (2.09 g, 91%).

Part B: To a solution of the cyclopropylmethylamine of part A (2.0 g, 4.4 mmol) in ethanol (12 mL) and THF (12 mL) was added NaOH (1.75 g, 44 mmol) in H₂O (10 mL), and the solution was heated to 65 degrees Celsius for 18 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to a pH value of 5. The resulting precipitate was collected by vacuum filtration to provide the acid as a white solid (1.58 g, 79%). HRMS calculated for C₂₂H₂₅NO₅S: 414.1375, found 414.1334.

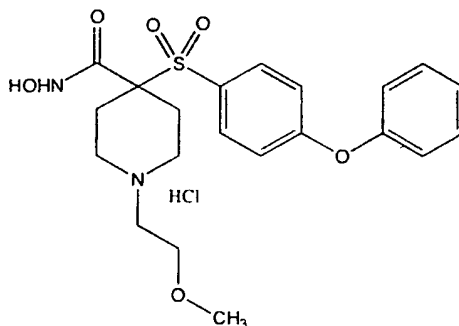
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Part C: To a solution of the acid of part B (1.58 g, 3.5 mmol) in dichloromethane (50 mL) was added triethylamine (1.46 mL, 10.5 mmol) followed by 50 percent aqueous hydroxylamine (2.3 mL, 35 mmol) and PyBroP (3.26 g, 6.99 mmol), and the solution was stirred at ambient temperature for 72 hours. The solution was washed with H₂O and saturated NaCl, and dried over magnesium sulfate. Reverse phase chromatography (on silica, acetonitrile/H₂O) provided the hydroxamate as a white solid (3.2 g, quantitative yield).

Part D: To a solution of the hydroxamate of part C (1.5 g, 3.5 mmol) in cold methanol (20 mL) was added acetyl chloride (0.25 mL, 3.5 mmol) in methanol (5 mL) and the solution was stirred at zero degrees Celsius for 15 minutes. After the solution had stirred for an additional 30 minutes at ambient temperature, it was concentrated in vacuo. Trituration with ethyl ether provided the title compound as a white solid (229 mg, 7 %).

Example 30: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[(4-phenoxyphenyl)-sulfonyl]-4-piperidine carboxamide, monohydrchloride

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Part A: To a solution of the amine HCl salt of part E, Example 6 (2.5 g, 5.87 mmol) and K₂CO₃ (1.6 g, 11.57 mmol) in N,N-dimethylformamide (25 mL) was
5 added 2-bromoethyl methyl ether (0.66 mL, 7.0 mmol) and then stirred at ambient temperature for 18 hours. Then N,N-dimethylformamide was evaporated under high vacuum and residue was diluted with ethyl acetate. The organic layer was washed with water and dried
10 over Mg₂SO₄. Concentration in vacuo provided the methoxyl ethyl amine as light yellow gel (2.63 g, quantitative yield).

Part B: To a solution of the methoxyl ethyl amine of part A (2.63 g, 5.87 mmol) in
15 tetrahydrofuran (18 mL) and ethanol (18 mL) was added NaOH (2.1 g, 5.25 mmol) in water (6 mL). The solution was heated to reflux for 12 hours. The solution was concentrated in vacuo and diluted with water. The aqueous layer was extracted with ether
20 (2X100 mL) and was acidified to pH=2. Vacuum filtration of the resulting precipitation provided the acid as a white solid (2.4 g, quantitative yield).

Part C: To a solution of the acid of part
25 B (2.0 g, 4.33 mmol), also containing N-methyl

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morpholine (1.8 mL, 16.4 mmol), and O-tetrahydro-2H-pyran-yl-hydroxylamine (0.767 g, 6.44 mmol) in N,N-dimethylformamide (20 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.1 g, 16.2 mmol), and solution was stirred at ambient temperature for 20 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with H₂O and dried over Mg₂SO₄. Concentration in vacuo provided the amide as off white foam (1.60 g, 71.1%).

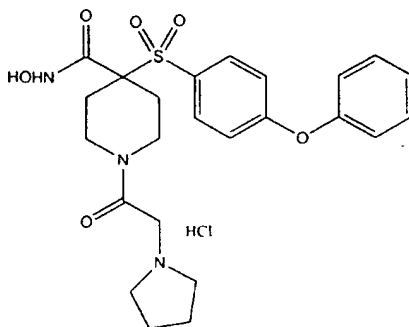
Part D: To a solution of the amide of part C (1.58 g, 3.05 mmol) in methanol (20 mL) cooled to zero degrees Celsius was added acetyl chloride (0.65 mL, 9.15 mmol) and the resulting solution was stirred at the same temperature for 3 hours. The solution was concentrated and reverse phase chromatography (on C-18 silica, acetonitrile/H₂O with 0.01% HCl) provided hydroxamate HCl salt as a white solid (0.65 g, 45.5%). Analytical calculation for C₂₁H₂₆N₂O₆S.HCl.0.75H₂O: C, 52.06; H, 5.93; N, 5.78; S, 6.62. Found: C, 51.94; H, 5.67; N, 5.91; S, 6.66. HSMS calculated for C₂₁H₂₆N₂O₆S: 435.1590, found 435.1571.

25

Example 31: Preparation of N-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-1-(1-pyrrolidinylacetyl)-4-piperidine carboxamide, monohydrochloride

30

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Part A: To a solution of the sulfone of
part D, Example 6 (2.75g, 5.6mmol) in
5 tetrahydrofuran (10mL) and ethanol (10mL) was added
NaOH (2.25g, 56mmol) in H₂O (20 mL), and the solution
was heated to 70 degrees Celsius for 20 hours. The
solution was concentrated in vacuo and the dry
residue was dissolved in H₂O. The aqueous layer was
10 extracted with ether and was acidified to pH=2
followed by the extraction with ethyl acetate. The
combined organic layers were washed again with H₂O and
dried over Mg₂SO₄. Concentration in vacuo provided
the BOC-acid as white foam (2.3g, 88.8%)

15 Part B: To a solution of BOC-acid of part
A (2.3g, 4.98mmol) in dichloromethane (6 mL) was
added trifluoroacetic acid (6 mL, 77.8 mmol), and the
resulting solution was stirred at ambient temperature
for 1 hour. Concentration in vacuo provided the
20 amine as white foam (2.44g, quantitative yield).

Part C: To the solution of the amine of
part B (2.4 g, 4.9 mmol) and triethylamine (3.5 mL,
24.4 mmol) in acetone (15 mL) and H₂O (15 mL) was
added chloroacetyl chloride (1.2 mL, 14.7 mmol), and
25 solution was stirred at ambient temperature for 20

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hours. Then acetone was evaporated and aqueous layer was acidified to pH=2. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with water and dried over Mg_2SO_4 .

- 5 Concentration in vacuo provided the chloroacetyl amide as light yellow gel (2.78 g, quantitative yield).

Part D: To the solution of the chloroacetyl amide of part C (2.78 g, 4.93mmol) and
10 K_2CO_3 (5 g, 36 mmol) in N,N-dimethylformamide (20 mL) was added pyrrolidine (3 mL, 36 mmol). The solution was then stirred at ambient temperature for 18 hours. Then N,N-dimethylformamide was evaporated under high vacuum and reverse phase chromatography (on C-18
15 silica, acetonitrile/ H_2O with 0.01% HCl) provided pyrrolidine acetyl amide (0.25g, 10.7%).

Part E: To a solution of the pyrrolidine acetyl amide of part D (0.25 g, 0.53 mmol), also containing N-methyl morpholine (0.14 mL, 1.27 mmol),
20 1-hydroxybenzotriazole (0.17 g, 1.2 mmol) and O-tetrahydro-2H-pyran-yl-hydroxylamine (0.15 g, 1.26 mmol) in N,N-dimethylformamide (4 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.23 g, 1.2 mmol). The solution was
25 then stirred at ambient temperature for 18 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated NaHCO_3 , H_2O and dried over Mg_2SO_4 . Concentration in vacuo
30 provided the THP amide as white foam (0.25 g, 83.3%).

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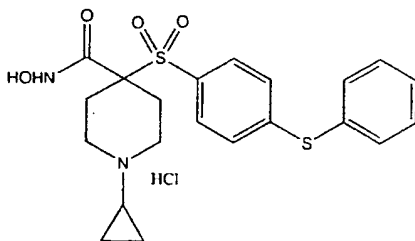
Part F: To a solution of the amide of part E (0.25 g, 0.437 mmol) in methanol (4 mL) cooled to zero degrees Celsius was added acetyl chloride (0.075 mL, 1.05 mmol), and the resulting solution was

5 stirred at ambient temperature for 2.5 hours. The solution was concentrated and reverse phase chromatography (on C-18 silica, acetonitrile/H₂O with 0.01% HCl) provided hydroxamate HCl salt as a white solid (80 mg, 29%). Analytical calculation for

10 C₂₄H₂₉N₃O₆S.HCl.0.9H₂O: C, 53.36; H, 5.98; N, 7.78. Found: C, 53.61; H, 5.71; N, 7.94. HSMS calculated for C₂₄H₂₉N₃O₆S: 488.1855, found 488.1835.

Example 32: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidine carboxamide,

15 monohydrochloride



20

Part A: A solution of 4-flurothiophenol (50.29 g, 0.39 mmol) in dimethylsulfoxide (500 mL) was heated to 65 degrees Celsius for 5 hours. The solution was cooled to ambient temperature and poured

25 into vigorously stirred ice water. The precipitate was filtered and washed twice with water. Drying

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under high vacuum provided the disulfide as a yellow oil (34.39 g, 68.9%) at ambient temperature.

Part B: A solution of di-tert-butyl dicarbonate (21.8 g, 0.1 mol) in tetrahydrofuran (5 mL) was added dropwise over 20 minutes to a solution of ethyl isonipecotate (15.7 g, 0.1 mol) in tetrahydrofuran (100 mL). The resulting solution was stirred overnight (about eighteen hours) at ambient temperature and concentrated in vacuo to yield a light oil. The oil was filtered through silica gel (ethyl acetate/hexane) and concentrated in vacuo to give the BOC-piperidine compound as a clear, colorless oil (26.2g, quantitative yield).

Part C: To a solution of BOC-piperidine compound of part B (15.96 g, 62 mmol) in tetrahydrofuran (300 mL), cooled to minus forty degrees Celsius, was added lithium diisopropylamide (41.33 mL, 74 mmol). The solution was then stirred at minus forty degrees C for one hour and zero degree C for one-half hour. Then the solution was cooled to minus forty degrees Celsius again and the disulfide of part A (15.77 g, 62 mmol) in tetrahydrofuran (20 mL) was added. The resulting solution as stirred at ambient temperature for 18 hours. The solution was diluted with H₂O and extracted with ethyl acetate. The organic layer was washed with H₂O and saturated NaCl and dried over MgSO₄. Chromatography (on silica, ethyl acetate/hexane) provided the sulfide as an oil (18 g, 75%).

Part D: To a solution of the sulfide of part C (16.5 g, 43 mmol) in dichloromethane (500 mL) cooled to zero degrees Celsius, was added m-chloroperbenzoic acid (18.5 g, 107 mmol). After 2
5 hours, the solution was diluted with dichloromethane and washed with 1N KOH, H₂O and dried over MgSO₄. Concentration in vacuo provided the sulfone as a solid (21 g, quantitative yield).

Part E: To a solution of sulfone (40 g, 96
10 mmol) of part D and powdered K₂CO₃ (26 g, 188 mmol) in N,N-dimethylformamide (200 mL) cooled to zero degrees Celsius was added thiolphenol (19.8 mL, 192 mmol), and the reculting composition was then stirred at ambient temperature for 36 hours. That solution was
15 concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with H₂O and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided phenyl thiophenyl Boc-sulfone as white solid
20 (44.34 g, 91%).

Part F: To a solution of phenyl thiophenyl Boc-sulfone of part E (8.6 g, 17 mmol) in dichloromethane (30 mL) cooled to zero degrees Celsius was added trifluroacetic acid (TFA; 30 mL),
25 and the resulting solution was stirred at ambient temperature for 2 hours. Concentration in vacuo provided the amine TFA salt as a light yellow gel (8.7 g, quantitative yield).

Part G: To a solution of amine TFA salt of
30 part F (6g, 11.9mmol) was added acetic acid (6.8 mL, 119mmol). After 5 minutes stirring at ambient

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temperature, (1-ethoxycyclopropyl)oxytriethylsilane (14.3 mL, 71.4 mmol) was added followed 5 minutes later by the addition of sodium cyanoboran hydrate (3.35 g, 53.55 mmol). Then the solution was heated to reflux for 18 hours. Methanol was evaporated and residue was washed with 1N NaOH, H₂O and dried over Mg₂SO₄. Concentration in vacuo gave the cyclopropylamine as an off-white powder (4.9 g, 92.6%).

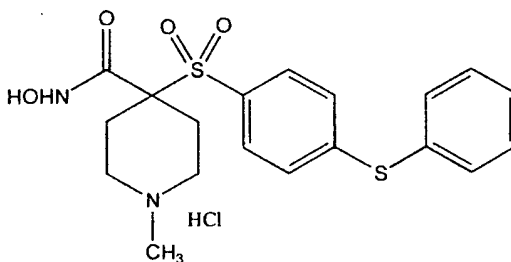
Part H: To a solution of the cyclopropylamine of part G (4.88 g, 10.95 mmol) in tetrahydrofuran (12.5 mL) and ethanol (12.5 mL) was added NaOH (4.3 g, 100 mmol) in water (25 mL). The solution was then heated to 50-55 degrees Celsius for 12 hours and was stirred at ambient temperature for 18 hours. Solution was acidified to pH=2 and concentration in vacuo provided the acid as white solid together with NaCl in the mixture. To a solution of this mixture in acetonitrile (50 mL) were added O-tetrahydropyrylamine (1.95 g, 16.3 mmol), N-methylmorpholine (2.4 mL, 21.9 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.14 g, 16.3 mmol) in sequence. The solution was then stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo and the residue was washed with H₂O and dried over Mg₂SO₄. Concentration in vacuo provided the tetrahydropyryl (THP) amide as white solid (3.0 g, 53.1%).

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Part I: To a solution of the THP amide of part H (3 g, 5.8 mmol) in methanol (45 mL) cooled to zero degrees Celsius was added acetyl chloride (1.5 mL, 21.1 mmol), and the solution was stirred at ambient temperature for 2.5 hours. Vacuum filtration of the precipitate provided hydroxamate HCl salt as a white solid (1.844 g, 68.3%). Analytical calculation for $C_{21}H_{24}N_2O_4S_2 \cdot HCl$: C, 53.78; H, 5.37; N, 5.97; S, 13.67. Found: C, 53.40; H, 5.26; N, 5.95; S, 13.68.

10

Example 33: Preparation of N-hydroxy-1-methyl-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



15

Part A: To a solution of amine TFA salt of part F, Example 32 (2.67 g, 5.14 mmol) and 37% formaldehyde in aqueous solution (2.0 mL, 25.7 mmol) in methanol (20 mL) was added borane pyridine (2.6 mL, 25.7 mmol) at ambient temperature. The solution was then stirred at ambient temperature for 18 hours. The solution was acidified to destroy excess reagent. Methanol was evaporated and the residue was partitioned between $NaHCO_3$ aqueous solution and ethyl acetate. The $NaHCO_3$ aqueous layer was extracted with ethyl acetate. The combined organic layers were

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washed with H₂O and dried over Mg₂SO₄. Concentration in vacuo gave the methyl amine as off white foam (1.6 g, 76%).

Part B: To a solution of the methyl amine of part A (1.63 g, 3.88 mmol) in ethanol (20 mL) was added KOH (1.31 g, 23.2 mmol) in water (4 mL), and the resulting solution was heated to 50 degrees Celsius for 8 hours, 70 degree Celsius for 4 hours and stirred at ambient temperature for 18 hours. The solution was acidified and concentrated in vacuo providing the acid as white solid together with NaCl in the mixture. To a solution of this mixture in N,N-dimethylformamide (50 mL) were added O-tetrahydropyrronylamine (0.92 g, 7.76 mmol), N-methylmorpholine (1.05 mL, 7.76 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.5 g, 7.76mmol) in sequence. The solution was stirred at ambient temperature for 72 hours. The solution was concentrated in high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated NaHCO₃, H₂O and dried over Mg₂SO₄. Concentration in vacuo and chromatography (silica, dichloromethane/methanol) provided the THP amide as white solid (0.46 g, 24.2%).

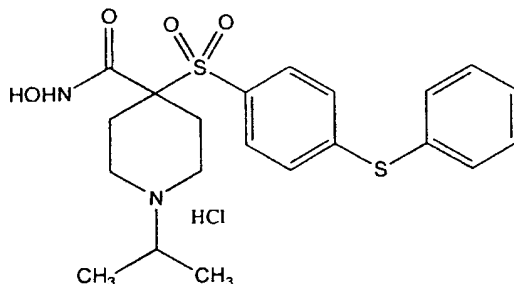
Part C: To a solution of the THP amide of part B (0.22 g, 0.45 mmol) in methanol (5 mL) cooled to zero degrees Celsius was added acetyl chloride (0.096 mL, 13.5 mmol), and the resulting solution was stirred at ambient temperature for 3 hours. The solution was concentrated in vacuo and reverse phase

chromatography (on C-18 silica, acetonitrile/H₂O with 0.01% HCl) provided hydroxamate HCl salt as a white solid (0.12 g, 60.6%). HSMS calculated for C₁₉H₂₂N₂O₄S₂: 407.1099, found 407.1105.

5

Example 34: Preparation of N-hydroxy-1-(1-methylethyl)-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride

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Part A: Into a solution of BOC-sulfone of part E, Example 32 (11.19 g, 22.12 mmol) in ethyl acetate (150 mL) cooled to zero degrees Celsius was bubbled HCl gas for 20 minutes. The solution was stirred at the same temperature for another 40 minutes. Concentration in vacuo and titration with ether provided the amine HCl salt (9.88 g, quantitative yield).

Part B: To a solution of amine HCl salt of part A (4.7 g, 10.6 mmol), triethylamine (2.0 mL, 14.4 mmol) and acetone (2.0 mL, 27.2 mmol) in dichloromethane (100 mL) were added sodium triacetoxylborohydride (5.7 g, 26.9 mmol) followed by acetic acid (1.5 mL, 26.9 mmol) at ambient

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temperature. The solution was stirred for 18 hours and then partitioned in 1N NaOH and ether. The aqueous layer was extracted with ether and combined organic layers were washed with 1N NaOH, H₂O and dried
5 over Mg₂SO₄. Concentration in vacuo gave the isopropyl amine as white foam (4.58 g, 96.2%).

Part C: To a solution of the isopropyl amine of part B (4.58 g, 10.2 mmol) in tetrahydrofuran (10 mL) and ethanol (10 mL) was added
10 NaOH (2.1 g, 5.25 mmol) in water (20 mL). The solution was heated to 60 degrees Celsius for 13.5 hours, then stirred at ambient temperature for 18 hours. The solution was acidified and concentrated in vacuo providing the acid as white solid together
15 with NaCl in the mixture. To a solution of this mixture in N,N-dimethylformamide (75 mL) were added 1-hydroxybenzotriazole (1.94 g, 14.4 mmol), O-tetrahydropyronylamine (1.8 g, 15.1 mmol), N-methylmorpholine (3.37 mL, 30.7 mmol), and 1-[3-
20 (dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.74 g, 14.3mmol) in sequence. The solution was stirred at ambient temperature for 48 hours. The solution was concentrated in high vacuum and the residue was dissolved in ethyl acetate. The
25 organic layer was washed with saturated NaHCO₃, H₂O and dried over Mg₂SO₄. Concentration in vacuo and chromatography (silica, dichloromethane/methanol) provided the THP amide as white solid (3.78 g, 71.3%).

30 Part D: To a solution of the THP amide of part C (1.15 g, 2.2 mmol) in methanol (20 mL) was

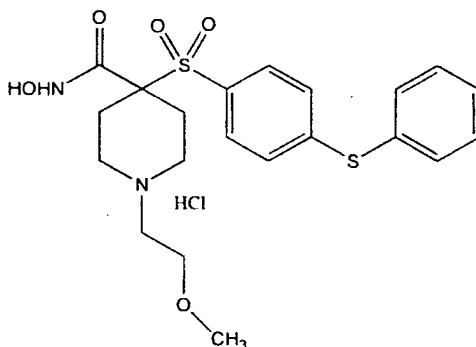
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added acetyl chloride (0.096 mL, 13.5 mmol), and the resulting solution was stirred at ambient temperature for 2.5 hours. The solution was concentrated in vacuo and reverse phase chromatography (on C-18 silica, acetonitrile/H₂O with 0.01% HCl) provided
5 hydroxamate HCl salt as a white solid (0.69 g, 66.3%). Analytical calculation for C₂₁H₂₆N₂O₄S₂.HCl.H₂O: C, 51.58; H, 5.98; N, 5.73; S, 13.11. Found: C, 51.76; H, 5.47; N, 5.72; S, 12.68.

10

Example 35: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-(phenylthio)phenyl]-sulfonyl]-4-piperidinecarboxamide,
monohydrochloride

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Part A: To the solution of the amine HCl
20 salt of part A, Example 34 (4.3 g, 9.43 mmol) and K₂CO₃ (2.62 g, 19.0 mmol) in N,N-dimethylformamide (40 mL) was added 2-bromoethyl methyl ether (1.9 mL, 20.2 mmol). The solution was stirred at ambient temperature for 48 hours. Then N,N-dimethylformamide
25 was evaporated under high vacuum and the residue was

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diluted with ethyl acetate. The organic layer was washed with water and dried over Mg_2SO_4 .

Concentration in vacuo provided the methoxyl ethyl amine as white foam (4.26 g, 95.3%).

5 Part B: To a solution of the methoxyl ethyl amine of part A (4.26 g, 9.2 mmol) in tetrahydrofuran (5 mL) and ethanol (5 mL) was added NaOH (3.7 g, 92.5 mmol) in water (9 mL). The solution resulting was heated to 60 degrees Celsius for 12 hours and stirred
10 at ambient temperature for 18 hours. The solution was concentrated in vacuo and diluted with water. The aqueous layer was extracted with ether (2X100 mL) and was acidified to pH=2. Vacuum filtration of the resulting precipitate provided the acid as a white
15 solid (3.5 g, 87.5%).

 Part C: To a solution of the acid of part B (3.4 g, 7.8 mmol), also containing N-methyl morpholine (2.6 mL, 23.4 mmol), 1-hydroxybenzotriazole (3.16 g, 23.4 mmol), and O-
20 tetrahydro-2H-pyran-2-yl-hydroxylamine (1.85 g, 15.5 mmol) in N,N-dimethylformamide (20 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (4.47 g, 23.4 mmol). The solution was stirred at ambient temperature for 36 hours. The
25 solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, H_2O and dried over Mg_2SO_4 . Concentration in vacuo provided the amide as off white solid (2.98 g, 71.5%).

30 Part D: To a solution of the amide of part C (2.98 g, 5.6 mmol) in methanol (40 mL) cooled to

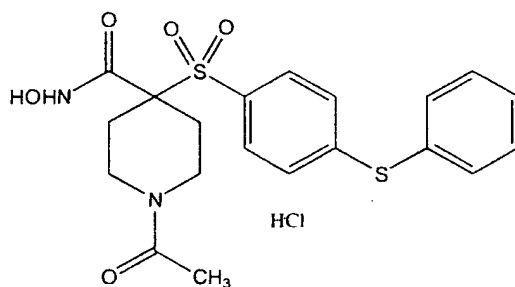
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zero degrees Celsius was added acetyl chloride (1.19 mL, 16.8 mmol), and the resulting solution was stirred at the ambient temperature for 3 hours. The solution was concentrated and reverse phase

5 chromatography (on C-18 silica, acetonitrile/H₂O with 0.01% HCl) provided hydroxamate HCl salt as a white solid (2.29 g, 84.6%). Analytical calculation for C₂₁H₂₆N₂O₆S.HCl.0.9H₂O: C, 50.12; H, 5.77; N, 5.57; S, 12.74. Found: C, 50.41; H, 5.85; N, 5.73; S, 12.83.

10

Example 36: Preparation of 1-acetyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-
piperidinecarboxamide, monohydrochloride



15

Part A: To a solution of the phenyl thiophenyl BOC-sulfone of part E, Example 32 (7 g, 1.29 mmol) in tetrahydrofuran (25 mL) and ethanol (25 mL) was added NaOH (5.1 g, 12.9 mmol) in H₂O (50 mL). The solution was heated to reflux for 20 hours. On cooling, the solution was concentrated in vacuo and the dry residue was dissolved in H₂O. The aqueous layer was extracted with ether and was acidified to

20 pH=2 followed by the extraction with ethyl acetate. The combined organic layers were washed again with H₂O

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and dried over Mg_2SO_4 . Concentration in vacuo provided the BOC-acid as white foam (3.9 g, 60%)

Part B: To a solution of BOC-acid of part A (2.3g, 4.98mmol) in dichloromethane (6 mL) was
5 added trifluoroacetic acid (6 mL, 77.8 mmol), and the solution was stirred at ambient temperature for 1 hour. Concentration in vacuo provided the amine as white foam (2.44g, quantitative yield).

Part C: To a solution of the amine of part
10 B (5.0 g, 12.08 mmol) and triethylamine (8.7 mL, 60.4 mmol) in acetone (20 mL) and H_2O (20 mL) cooled to zero degrees Celsius was added acetyl chloride (4.6 mL, 36 mmol), and the solution was stirred at ambient temperature for 40 hours. The acetone was evaporated
15 and the aqueous layer was acidified to pH=2. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water and dried over Mg_2SO_4 . Concentration in vacuo provided the acetyl amide as light yellow foam (5 g,
20 quantitative yield).

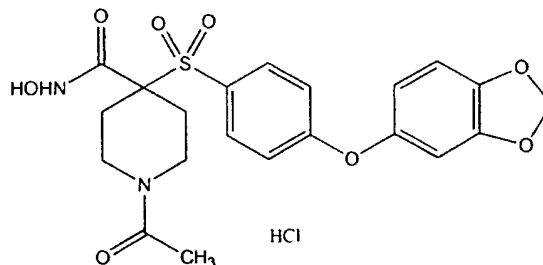
Part D: To a solution of acetyl amide of part C (5 g, 11.9 mmol), also containing N-methyl morpholine (5.3 mL, 47.6 mmol), 1-hydroxybenzotriazole (4.8 g, 35.7 mmol) and O-
25 tetrahydro-2H-pyran-yl-hydroxylamine (2.8 g, 23.5 mmol) in N,N-dimethylformamide (50 mL) was added 1-[3(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (6.8 g, 35.7 mmol), and the solution was stirred at ambient temperature for 20 hours. The
30 solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic

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layer was washed with saturated NaHCO_3 , KHSO_4 , H_2O and dried over Mg_2SO_4 . Concentration in vacuo provided the THP amide as white foam (6.07 g, 98.2%).

Part E: To a solution of the THP amide of
5 part D (6.07 g, 11.7 mmol) in methanol (100 mL) cooled to zero degrees Celsius was added acetyl chloride (2.5 mL, 35.1 mmol), and the solution was stirred at ambient temperature for 3 hours. The solution was concentrated and chromatography (on
10 silica, methanol/ dichloromethane) provided hydroxamate HCl salt as a white solid (3.3 g, 65%). Analytical calculation for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_6\text{S} \cdot \text{HCl} \cdot 0.9\text{H}_2\text{O}$: C, 53.36; H, 5.98; N, 7.78. Found: C, 53.61; H, 5.71; N, 7.94. HSMS calculated for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_6\text{S}$: 488.1855,
15 found 488.1835.

Example 37: Preparation of 1-acetyl-4-[[4-(1,3-benzodioxol-5-yloxy)phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide,
20 monohydrochloride



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Part A: To a solution of sulfone from Part D, Example 32 (25g, 67.3 mmol) and powdered K_2CO_3 (23.3 g, 16.9 mmol) in N,N-dimethylformamide was added sesamol (23.24 g, 16.8 mmol) at ambient temperature, and solution was heated to ninety degrees Celsius for 24 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H_2O and dried over $MgSO_4$. Chromatography (on silica, ethyl acetate/hexane) provided sesamol BOC-sulfone as a white foam (33.6 g, 93.6%).

Part B: To a solution of sesamol BOC-sulfone of part E (29.31 g, 54.93 mmol) in ethanol (60 mL) and tetrahydrofuran (60 mL) was added NaOH (21.97 g, 544 mmol) from addition funnel over 20 minutes at ambient temperature. The solution was then heated to sixty degrees Celsius for 9 hours, then ambient temperature for 12 hours. The solution was concentrated in vacuo and diluted with water. The aqueous layer was extracted with ether and acidified to pH=2. It was then extracted with ethyl acetate and the combined organic layers were washed with H_2O and dried over $MgSO_4$. Concentration in vacuo provided the acid as white solid (25.3, 91%).

Part C: HCl gas was bubbled into a solution of the acid of part F (20.3 g, 40.15 mmol) in ethyl acetate cooled to zero degrees Celsius. After 1.5 hours, vacuum filtration of white precipitate provided the amine HCl salt as a white solid (16 g, 93.6%).

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Part D: To the solution of the amine HCl salt of part G (8.1 g, 19.01 mmol) and triethylamine (13.2 mL, 95.05 mmol) in acetone (150 mL) and H₂O (150 mL) cooled to zero degrees Celsius was added acetyl chloride (5.4 mL, 76 mmol). The solution was stirred at ambient temperature for 18 hours. The acetone was evaporated and aqueous layer was acidified to pH=2. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water and dried over Mg₂SO₄. Concentration in vacuo provided the acetyl amide as light yellow foam (9.24 g, quantitative yield).

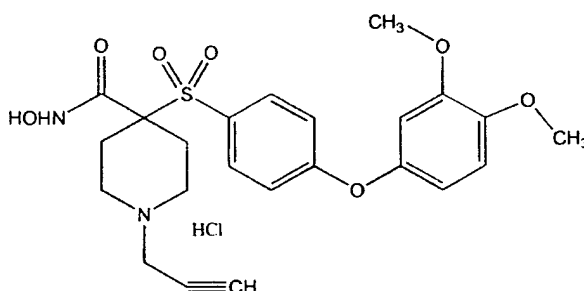
Part E: To the solution of the acetyl amide of part D (9.1 g, 20.33 mmol), N-methyl morpholine (6.7 mL, 61 mmol), 1-hydroxybenzotriazole (8.2 g, 60 mmol) and O-tetrahydro-2H-pyran-yl-hydroxylamine (4.85 g, 40 mmol) in N,N-dimethylformamide (40 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (11.65 g, 60 mmol). The resulting solution was stirred at ambient temperature for 20 hours. The solution was then concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated NaHCO₃, KHSO₄, H₂O and dried over Mg₂SO₄. Concentration in vacuo and chromatography (on silica, ethyl acetate/hexane) provided the THP amide as white a foam (10 g, 89.7%).

Part F: To a solution of 4N HCl in dioxane (20 mL) was added a solution of the amide of part E (5.0 g, 9.1 mmol) in methanol (5 mL) and dioxane (15

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mL). That solution was stirred at ambient temperature for 30 minutes. Vacuum filtration of the white precipitate provided the hydroxamate HCl salt as a white solid (3.3 g, 65%). Analytical calculation for $C_{21}H_{22}N_2O_8S \cdot HCl$: C, 54.34; H, 5.15; N, 5.49; S, 6.43. Found: C, 54.54; H, 4.79; N, 6.06; S, 6.93. HSMS calculated for $C_{21}H_{22}N_2O_8S$: 463.1175, found 463.118.

10 Example 38: Preparation of 4-[[4-(3,4-dimethoxyphenoxy)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride



15

Part A: HCl gas was bubbled into a solution of the sulfone of part D, Example 32 (10 g, 24 mmol) in ethyl acetate cooled to zero degrees Celsius. After 4 hours, vacuum filtration of the white precipitate provided the amine HCl salt as a white solid (7.27 g, 86%).

Part B: To a solution of the amine HCl salt of part A (5.98 g, 17 mmol) and powered K_2CO_3 (4.7 g, 34 mmol) in N,N-dimethylformamide (120 mL) was added propargyl bromide (2.022 g, 17 mmol) at

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ambient temperature, followed by stirring for 4 hours. The solution was diluted with ethyl acetate and washed with H₂O, saturated NaCl and dried over Mg₂SO₄. Concentration *in vacuo* and chromatography (on silica, ethyl acetate/hexane) provided the propargyl amine as a white solid (5.2 g, 86%).

Part C: To a solution of the propargyl amine of part B (8 g, 22.63 mmol) and powdered K₂CO₃ (8.8 g, 56.6 mmol) in N,N-dimethylformamide (150 mL) was added 3,4-dimethoxyphenol (6.98 g, 45 mmol) at ambient temperature. The composition was heated to 90 degrees Celsius for 36 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N NaOH, H₂O and dried over MgSO₄. Chromatography (on silica, ethyl acetate/hexane) provided phenoxy propargyl amine as light yellow gel (10 g, 90.9%).

Part D: A solution of NaOH (8.2 g, 200 mmol) in H₂O (30 mL) from addition funnel was added to a solution of the phenoxy propargyl amine of part C (10 g, 20.5 mmol) in ethanol (15 mL) and tetrahydrofuran (15 mL) at ambient temperature. The resulting solution was then heated to 60 degrees Celsius for 48 hours and at ambient temperature for 48 hours. The solution was concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with ether and acidified to pH=2. Vacuum filtration of the white precipitate provided the acid as a white solid (9.4 g, quantitative yield).

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Part E: To a solution of the acid of part D (9.4g, 20.5 mmol), N-methyl morpholine (6.8 mL, 62 mmol), 1-hydroxybenzotriazole (8.3 g, 60 mmol) and O-tetrahydro-2H-pyran-yl-hydroxylamine (4.8 g, 40 mmol) in N,N-dimethylformamide (50 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (11.7 g, 60 mmol). The resulting solution was then stirred at ambient temperature for 20 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with saturated NaHCO₃, H₂O and dried over Mg₂SO₄. Concentration in vacuo and chromatography (on silica, ethyl acetate/hexane) provided the THP amide as white foam (10 g, 89.7%).

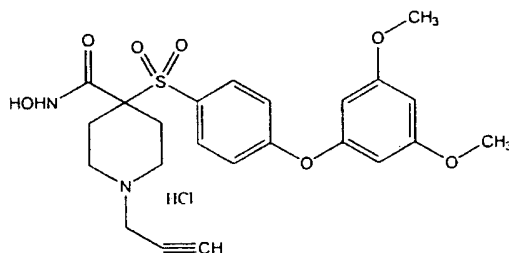
Part F: To a solution of 4N HCl in dioxane (38 mL, 152 mmol)) was added a solution of the amide of part E (8.5 g, 15.2 mmol) in methanol (8 mL) and dioxane (24 mL). The resulting composition was stirred at ambient temperature for 80 minutes. Concentration in vacuo and titration with ether provided hydroxamate HCl salt as a white solid (7.7 g, quantitative yield). HSMS calculated for C₂₃H₂₆N₂O₇S: 475.1461, found 475.1539.

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Example 39: Preparation of 4-[[4-(3,5-dimethoxyphenoxy)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride

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Part A: To a solution of the propargyl
amine of Part B, Example 38 (2 g, 5.6 mmol) and
5 powdered K₂CO₃ (1.9 g, 13.7 mmol) in N,N-
dimethylformamide (20 mL) was added 3,5-
dimethoxyphenol (2.18 g, 13.7 mmol) at ambient
temperature. The resulting composition was heated to
90 degrees Celsius for 36 hours. The solution was
10 concentrated under high vacuum and the residue was
dissolved in ethyl acetate. The organic layer was
washed with 1N NaOH, H₂O and dried over MgSO₄.
Chromatography (on silica, ethyl acetate/hexane)
provided phenoxy propargyl amine as light yellow gel
15 (2.76 g, quantitative yield).

Part B: To a solution of the phenoxy
propargyl amine of part A (2.75 g, 5.6 mmol) in
ethanol (5 mL) and tetrahydrofuran (5 mL) was added
NaOH (2.3 g, 56 mmol) in H₂O (10 mL) at ambient
20 temperature. The solution was then heated to 60
degrees Celsius for 18 hours. The solution was
concentrated in vacuo and diluted with water. The
aqueous layer was extracted with ether and acidified
to pH=2. Vacuum filtration of white precipitate
25 provided the acid as white solid (2 g, 77.2%).

Part C: To a solution of the acid of part
B (2 g, 4.3 mmol), also containing N-methyl

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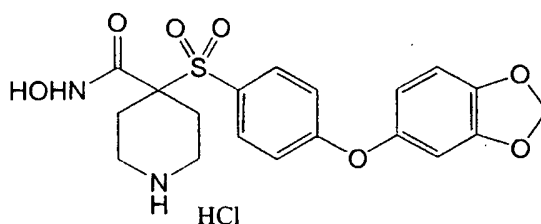
morpholine (1.9 mL, 17.2 mmol), 1-hydroxybenzotriazole (1.74 g, 13.2 mmol) and O-tetrahydro-2H-pyran-yl-hydroxylamine (1.02 g, 8.6 mmol) in N,N-dimethylformamide (20 mL) was added 1-
5 [3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.47 g, 12.9 mmol). The resulting composition was stirred at ambient temperature for 20 hours. The solution was concentrated under high vacuum and the residue was dissolved in ethyl
10 acetate. The organic layer was washed with saturated NaHCO₃, H₂O and dried over Mg₂SO₄. Concentration in vacuo and chromatography (on silica, ethyl acetate/hexane) provided the THP amide as white foam (2.4 g, quantitative yield).

15 Part D: To a solution of 4N HCl in dioxane (13 mL, 52 mmol)) was added a solution of the THP amide of part C (2.43 g, 4.35 mmol) in methanol (2 mL) and dioxane (6 mL), and the composition was stirred at ambient temperature for 80 minutes.
20 Vacuum filtration of the precipitate and washing with ether provided the hydroxamate HCl salt as a white solid (1.25 g, 56.3%). Analytical calculation for C₂₃H₂₆N₂O₇S.1.5HCl: C, 52.20; H, 5.24; N, 5.29. Found: C, 52.00; H, 5.05; N, 5.17.

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Example 40: Preparation of 4-[[4-(1,3-benzodioxol-5-yloxy)phenyl]sulfonyl]-N-hydroxy-4-
piperidinecarboxamide, monohydrochloride

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Part A: To a solution of the N-BOC
carboxylic acid compound of part B, Example 37 (1.25
5 g, 2.47 mmol), N-methylmorpholine (1.00 g, 9.89 mmol)
and 1-hydroxybenzotriazole hydrate (0.40 g, 2.96
mmol) in N,N-dimethylformamide (8 mL) at ambient
temperature was added 1-(3-dimethylaminopropyl)-3-
ethylcarbodiimide hydrochloride (0.616 g, 3.21 mmol).
10 After 5 minutes a solution of O-tetrahydro-2H-pyran-
2-yl-hydroxylamine (0.39 g, 3.33 mmol) in N,N-
dimethylformamide (2 mL) was added. After 2 days the
pale yellow solution was concentrated *in vacuo* to
afford a residue which was dissolved in ethyl acetate
15 and washed successively with water (3X) and brine and
dried over sodium sulfate. Concentration afforded a
residue that was chromatographed on silica gel
eluting with ethyl acetate/hexane (20/80) to afford
the THP-protected hydroxamate as an oil (1.54 g,
20 100%).

Part B: To a solution of THP-protected
hydroxamate of part A (1.49 g, 2.46 mmol) in dioxane
(9 mL) and methanol (3 mL) was added 4 N HCl in
dioxane (10 mL, 40 mmol). After 1.5 hours at ambient
25 temperature the suspension was treated with diethyl
ether (15 mL) and filtered to afford the title
hydroxamate (1.00 g, 89%) as a colorless powder. MS

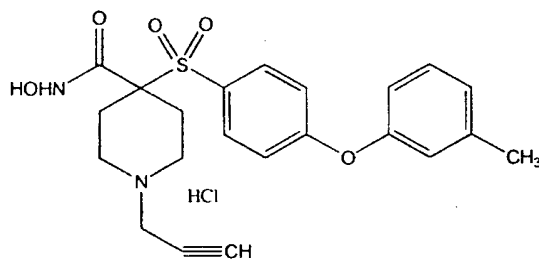
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(CI) MH^+ calculated for $C_{19}H_{20}N_2SO_7$: 421, found 421.
Analytical calculation for $C_{19}H_{20}N_2SO_7 \cdot HCl$: C, 49.95;
H, 4.63; N, 6.13; Cl, 7.76; S, 7.02. Found: C,
49.82; H, 4.60; N, 5.98; Cl, 17.38; S, 7.10.

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Example 41: Preparation of N-hydroxy-4-[[4-(3-methylphenoxy)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide,
monohydrochloride

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Part A: To a solution of propargylamine of
15 part F, Example 9 (8.0 gm, 22.6 mmol) and K_2CO_3 in
N,N-dimethylformamide (30 mL) was added m-cresol (3.5
g, 33.9 mmol) and the solution was stirred at 90
degrees Celsius for 18 hours. The solution was
diluted with H_2O and extracted with ethyl acetate. The
20 combined organic layers were washed with saturated
NaCl and dried over $MgSO_4$. Chromatography (on silica,
eluting with 10% ethyl acetate/hexane) provided the
3-methyl phenoxyphenyl compound as a solid (10.3 g,
98%). Cal'd MS for $C_{24}H_{29}NSO_5$ 441.1688, found 442.1697

25

Part B: To a solution of 3-methyl
phenoxyphenyl compound of part A (10.3 g, 22.0 mmol)
in tetrahydrofuran (50 mL) and ethanol (50 mL) was

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added NaOH (8.9 g, 22.3 mol) and the solution was heated at 65 degrees Celsius for 24 hours. The solution was concentrated *in vacuo* and the aqueous residue was acidified to pH=3. Vacuum filtration of the resulting precipitate provided the acid as a white solid (9.0 g, 91%). MS cal'd for $C_{22}H_{24}NSO_5$ = 414.1375. Found = 414.1389.

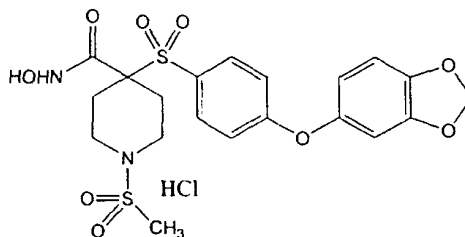
Part C: To a solution of the acid of part B (9.0 g, 19.5 mmol) was added 1-hydroxybenzotriazole (3.24 g, 23.9 mmol), N-methylmorpholine (6.58 mL, 59.9 mmol), O-tetrahydro-2H-pyran-yl-hydroxylamine (3.5 g, 29.9 mmol) followed by 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (5.35 g, 27.9 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H_2O (400 mL) and extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried over $MgSO_4$. Chromatography (on silica, eluting with 40% ethyl acetate/hexane) provided the desired THP-protected hydroxamate as a solid (6.9 g, 67%). Analytical calculation for $C_{27}H_{33}N_2SO_6 \cdot 0.1 H_2O$: C, 62.92, H, 6.49, N, 5.43, S, 6.23. Found: C, 62.69, H, 6.47, N, 5.57, S, 6.33. Cal'd MS for $C_{27}H_{33}N_2SO_6$: 513.2059. Found 513.2071.

Part D: To a solution of THP-protected hydroxamate of part C (6.4 gm, 12.5 mmol) in dioxane (56 mL) and methanol (19 mL) was added 4 N HCl/dioxane (40 mL). After stirring at ambient temperature for 1 hours, the solution was concentrated *in vacuo*. Trituration with ethyl ether

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provided the title compound as a white solid (5.66 g, 97.4%). Cal'd MS for $C_{22}H_{24}N_2SO_5+1$: 429.1484.. Found M+1: 429.1493

- 5 Example 42: Preparation of 4-[[4-(1,3-benzodioxol-5-yloxy)phenyl]sulfonyl]-N-hydroxy-1-
(methylsulfonyl)-4-piperidinecarboxamide



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- Part A: To a solution of sulfone of part D, Example 32 (25.g, 67.3 mmol) in N,N-dimethylformamide was added potassium carbonate (23.3 g, 0.169 mol) and sesamol (23.2 g, 0.164 mol). The solution was submerged in an oil bath at 90°C and stirred for 25 hours. Ethyl acetate was added to the solution, and the organic phase was washed with water, 1N NaOH and water, dried over magnesium sulfate, filtered and concentrated in vacuo.
- 15
- 20 Chromatography on silica, eluting with ethyl acetate/hexane (15/85) provided the ethyl ester compound as an oil (29.3 g, 82%).

- Part B: To a solution of ethyl ester from part A (29.3 gm, 54.93 mmol) in ethanol (60 mL) and tetrahydrofuran (60 mL) was added a solution of NaOH (21.9 g, 0.549 mol) in water 120 mL) and the solution was heated at 65 degrees Celsius for 10 hours. The
- 25

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solution was concentrated in vacuo and the aqueous residue was acidified to pH=3. The solution was extracted with ethyl acetate. The solution was dried over magnesium sulfate, filtered and concentrated in vacuo to give the acid as a yellow foam (25.6 g 92.1%).

Part C: To a solution of the acid of Part B (20.3 g, 40.15 mmol) in ethyl acetate at zero degrees C was bubbled gas HCl for 20 minutes. The solution stirred at Zero degrees Celsius for 1.5 hours. The precipitate formed was filtered and washed with ether to give the amine hydrochloride as a white solid (16.0 g, 93.5%)

Part D: To a solution of amine hydrochloride of part C (7.5g, 17.0 mmol) in methylene chloride (200 mL) was added methanesulfonyl chloride (2.0 g, 25.0 mol) and the solution was stirred at ambient temperature for 18 hours. The solution was washed with water and saturated NaCl, dried over magnesium sulfate, concentrated in vacuo to provide the acid as a white solid (6.97g, 85%).

Part E: To a solution of the acid of part D (7.37 g, 15.0 mmol) was added 1-hydroxybenzotriazole (2.43 g, 18.0 mmol), N-methylmorpholine (4.94 mL, 45.0 mmol), O-tetrahydro-2H-pyran-yl-hydroxylamine (2.65 g, 22.5 mmol) followed by 1-3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (4.02 g, 21.0 mmol). The solution was stirred at ambient temperature for 18 hours. The solution was diluted with H₂O (400 mL) and extracted with ethyl acetate. The organic layer

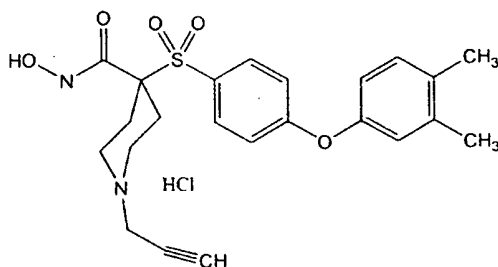
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was washed with saturated NaCl and dried over MgSO_4 . Chromatography (on silica, eluting with 50% ethyl acetate/hexane) provided the desired THP-protected hydroxamate as a solid (7.54 g, 85%).

5 Part F: To a solution of THP-protected hydroxamate of part E (6.32 gm, 10.8 mmol) in dioxane (75 mL) and methanol (25 mL) was added 4 N HCl/dioxane (30 mL). After stirring at ambient temperature for 1 hour, the solution was concentrated
10 in vacuo. Trituration with ethyl ether provided the title compound. Chromatography (on silica, 5% methanol/ethyl acetate) provided the hydroxamate as a white solid (4.32 g, 80%) Cal'd MS for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{S}_2\text{O}_9$ +1: 499.0845. Found 499.0848.

15

Example 43: Preparation of 4-[[4-(3,4-Dimethylphenoxy)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monhydrochloride



20

Part A: A mixture of the fluoro compound from part F, Example 9 (2.0 g, 5.66 mmol), 3,4-dimethylphenol (2.0 g, 16.5 mmol), and potassium
25 carbonate (2.3 g, 16.5 mmol) in N,N-dimethylformamide (15 mL) was heated at 90 degrees Celsius overnight

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(about 18 hours) under an atmosphere of nitrogen. The brown mixture was concentrated *in vacuo* and purified by chromatography (on silica, ethyl acetate/hexane) to afford the 3,4-dimethylphenoxy phenyl compound as a clear, yellow oil (2.0 g, 79% yield). Analytical calculation for $C_{25}H_{29}NO_5S$: C, 65.91; H, 6.42; N, 3.04; S, 7.04. Found: C, 65.76; H, 6.37; N, 3.03; S, 7.00.

Part B: A solution of the 3,4-dimethylphenoxy phenyl compound of part A (2.0, 4.93 mmol) and potassium hydroxide (1.7 g, 29.7 mmol) in a mixture of ethanol (25 mL) and water (4 mL) was stirred at reflux for four hours under a nitrogen atmosphere. The solution was cooled with an ice bath, subsequently acidified with concentrated hydrochloric acid, and concentrated to a crude residue. The crude residue, O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.88 g, 7.50 mmol), triethylamine (0.81 mL, 5.81 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in acetonitrile (24 mL) was stirred at ambient temperature overnight. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, a saturated sodium bicarbonate solution, water, and a saturated salt solution. After drying over magnesium sulfate, the filtrate, as the THP-protected hydroxamate, was concentrated to a yellow foam.

Part C: The THP-protected hydroxamate (920 mg, 1.75 mmol) of part B was dissolved in methanol (16 mL). Acetyl chloride (0.37 mL, 5.3 mmol) was

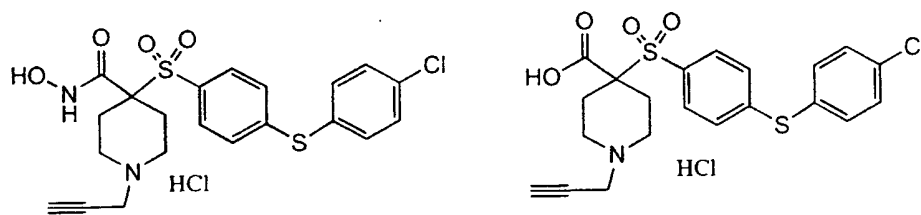
-384-

added. After three hours, concentration followed by reverse phase HPLC afforded the title compound as a white solid (611 mg, 79%). MS (EI) MH^+ calculated for $C_{23}H_{26}N_2O_5S$: 443, found 443.

5

Example 44: Preparation of 4-[[4-(4-chlorophenyl)thiophenyl]sulfonyl]-1-(propynyl)-4-piperidinecarboxylic acid, monohydrochloride and 4-[[4-(4-chlorophenyl)thiophenyl]sulfonyl]-
10 N-hydroxy-1-(propynyl)-4-piperidinecarboxamide, monohydrochloride

15



Part A: A mixture of the fluoro compound from part F, Example 9 (2.0 g, 5.66 mmol), 4-chlorothiophenol (1.0 g, 6.94 mmol), and potassium carbonate (1.1 g, 8.00 mmol) in N,N-dimethylformamide (12 mL) was stirred overnight (about 18 hours) under an atmosphere of nitrogen at ambient temperature. The mixture was concentrated in vacuo. The residue was diluted with water and extracted with ethyl
20 acetate. The organic layer was washed with water and a saturated salt solution, dried over magnesium sulfate, and concentrated in vacuo to a yellow oil.

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The oil was purified by chromatography (on silica, ethyl acetate/hexane) to afford the 4-chlorophenylthiolphenyl compound as a white solid (2.0 g, 75% yield). Analytical calculation for

5 $C_{23}H_{24}NO_4S_2Cl$: C, 57.791; H, 5.06; N, 2.93; S, 13.42; Cl, 7.42. Found: C, 57.57; H, 5.11; N, 2.94; S, 13.19; Cl, 7.73.

Part B: The chlorophenylthiophenyl compound from part A (2.04 g, 4.27 mmol) was diluted with

10 ethanol (30 mL) and water (5mL). Potassium hydroxide (1.55 g, 27.7 mmol) was added, and the mixture was heated at reflux for 3 hours. After complete reaction, the solution was cooled and was acidified to pH=1-3 with concentrated HCl. The solvent was

15 removed by rotary evaporation and the residue was azeotroped to dryness by repeated addition of acetonitrile. The acid hydrochloride was further dried on a vacuum line, then carried as is through the coupling reaction. The saponification was

20 presumed to be quantitative.

Part C: The carboxylic acid hydrochloride from the previous step (4.27 mmol) was suspended in acetonitrile (20 mL). N-Methylmorpholine (about 1.0 mL) was added, followed by O-tetrahydro-2H-pyran-2-

25 yl-hydroxylamine (585 mg, 5 mmol). After 5 minutes, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC; 955 mg, 5 mmol) was added. The mixture was stirred overnight (about 18 hours), then solvent was removed by rotary evaporation, the

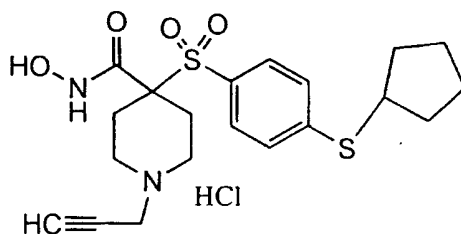
30 residue was diluted with half-saturated $NaHCO_3$ solution (50 mL), and the product was extracted into

ethyl acetate (2 X100 mL). In this example, an intractable emulsion complicated compound recovery. The combined organic layers were dried over MgSO_4 , filtered through silica, concentrated, and subjected to chromatography (flash silica, ethyl acetate/hexane) affording, on concentration, the title O-THP-protected hydroxamate (162 mg, 7%, from ester) as a foam. MS (EI) MH^+ calculated for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4\text{S}_2\text{Cl}$: 450, found 450. Because mass recovery was poor, the silica filter cake was extracted with 1:1 methanol:ethyl acetate affording 4-[[4-(4-chlorophenyl)thiolphenyl]sulfonyl]-1-(propynyl)-4-piperidinecarboxylic acid, monohydrochloride (540 mg, 26%)

Part D: The O-THP-protected hydroxamate of part C (441 mg, 0.80 mmol) was dissolved in methanol (2 mL). Acetyl chloride (0.2 mL, 3 mmol) was added. After three hours, concentration followed by reverse phase HPLC afforded the title hydroxamate compound as a pink solid (162 mg, 44%). MS (EI) MH^+ calculated for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4\text{S}_2$: 465, found 465.

Example 45: Preparation of 4-[[4-(Cyclopentylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide, monohydrochloride

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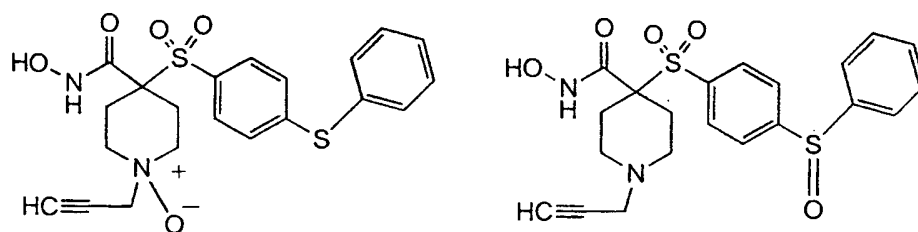
Part A: The propargyl amine of part F, Example 9 (3.05 g, 8.5 mmol) was combined with K_2CO_3 (1.38 g, 10 mmol), N,N-dimethylformamide (6 mL) and cyclopentyl mercaptan (1.02 mL, 10 mmol). The mixture was heated to 80 degrees Celsius for 4 hours and 95 degrees Celsius for 2.5 hours, monitoring by TLC. Aqueous workup was accomplished using water (10 mL) and ethyl acetate (2 X 100 mL). The combined organic layers were dried over magnesium sulfate, concentrated, and chromatographed (flash silica; ethyl acetate/hexane eluant) affording the cyclopentylmercaptyl compound as an oil (3.2 g, 86%)

Part B: The cyclopentylmercaptyl compound from part A (3.12 g 7.13 mmol) was diluted with ethanol (50 mL) and water (8 mL). Potassium hydroxide (2.59 g, 46.3 mmol) was added, and the mixture was heated at reflux for 3.5 hours. After complete reaction, the solution was cooled and was acidified to pH=1-3 with concentrated HCl. The solvent was removed by rotary evaporation and the residue was azeotroped to dryness by repeated addition of acetonitrile. The carboxylic acid hydrochloride was further dried on a vacuum line, then carried as is through the coupling reaction. The saponification was presumed to be quantitative.

Part C: The carboxylic acid hydrochloride from Part B (7.13 mmol) was suspended in acetonitrile (50 mL). N-Methylmorpholine (ca. 2.0 mL) was added, followed by O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.05 g, 9 mmol). After 5 minutes, EDC (1.72 g, 9 mmol) was added. The mixture was stirred overnight (about 18 hours), then solvent was removed by rotary evaporation. The residue was diluted with half-saturated NaHCO₃ solution (50 mL), and the product was extracted into ethyl acetate (2 X100 mL). The combined organic layers were dried over MgSO₄, filtered through silica, concentrated, and subjected to chromatography (flash silica, ethyl acetate/hexane) affording, on concentration, the O-THP-protected hydroxamate (2.0 g, 51%, from ester) as a foam.

Part D: The O-THP-protected hydroxamate from Part D (2.00 g, 3.95 mmol) was dissolved in methanol (16 mL). Acetyl chloride (0.86 mL, 12 mmol) was added over 2 minutes. The reaction was stirred at ambient temperature for 4 hours, then concentrated, with repeated addition of chloroform and acetonitrile to effect drying. The title compound precipitated as a white solid (1.77 g, 98%). MS (EI) MH⁺ calculated for C₂₀H₂₆N₂O₄S₂: 422, found 422.

Example 47: Preparation of N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, 1-oxide and N-hydroxy-4-[[4-(phenylsulfinyl)-phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide

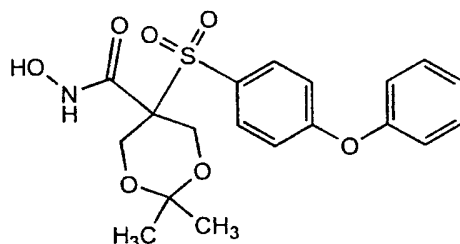


m-Chloroperbenzoic acid (57-86%, 120 mg) was added to a solution of N-hydroxy-4-[[4-(phenylthio)phenyl]-sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide (title compound, Example 9) (215 mg, 0.5 mmol) in methanol (5 mL) at zero degrees Celsius. The reaction was permitted to warm slowly to ambient temperature and after 16 hours, the mixture was passed through a micron filter and concentrated. Reverse phase HPLC (Delta Pak 50 X 300 mm; 15 micron C₁₈ 100 Angstrom; 30 minute gradient method starting with dilute HCl (0.5 mL/4 L): acetonitrile 80:20, ending with 50:50) separated 5 major components. The first and second peaks off the column afforded, upon concentration, 14 (6%) and 16 mg (7%) of two compounds, which were assigned as diastereomers of N-Hydroxy-4-[[4-(phenylsulfinyl)-phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide on the basis of their NMR

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spectra. The third peak was unidentified. The 4th peak was assigned by NMR as N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, 1-oxide (147 mg, 66%) MS (EI) 5 MH^+ calculated for $C_{21}H_{22}N_2O_5S_2$: 447, found 447. The last peak contained 73 mg of recovered 3-chlorobenzoic acid.

Example 48: Preparation of N-hydroxy-2,2-dimethyl-
10 5-[(4-phenoxyphenyl)sulfonyl]-
1,3-dioxane-4-carboxamide



15 Part A: A fresh sodium methoxide solution was prepared by slowly adding hexane-washed sodium spheres (9.4 g, 410 mmol) to methanol (1.0 L) at zero degrees Celcius. To this cooled solution was added the 4-fluorothiophenol (50.0 g, 390 mmol) followed by
20 methyl 2-chloro acetate (42.3 g, 390 mmol). After warming to ambient temperature the reaction was stirred overnight (about 18 hours). The methanol was removed in vacuo and the residue was taken up in ethyl acetate (300 mL). The organic layer was washed
25 with water (2x-200 mL) and dried over $MgSO_4$.

Concentrating afforded the methyl ester sulfide product as a clear oil (71.8 g, 92%).

Part B: To a solution of the methyl ester sulfide product of part A (71.8 g, 358 mmol) in 70% methanol/H₂O (1.0 L) was slowly added Oxone™ (660 g, 1.08 mol). The mixture stirred overnight (about 18 hours) at ambient temperature. The excess Oxone™ was filtered off and the methanol was removed from the filtrate in vacuo. The remaining aqueous solution was extracted with ethyl acetate (3x 300 mL). The organic layers were washed with water (2x-300 mL) and dried over MgSO₄. Concentrating afforded the sulfone product as a tan oil (82 g, 98%).

Part C: To a prepared slurry of potassium bicarbonate (1.0 g, 9.8 mmol) in 37% formaldehyde solution was added the sulfone product of part B (28.6 g, 123 mmol). The reaction was stirred for one hour and then a saturated solution of sodium sulfate (20 mL) was added. After stirring for thirty minutes, the mixture was extracted with diethyl ether (4x-100 mL). The organic layers were dried over MgSO₄. Chromatography (on silica, ethyl acetate/hexane) provided the sulfone diol product as a clear oil (15.3 g, 42%).

Part D: The sulfone diol product of Part C (1.3 g, 4.5 mmol) was dissolved in acetone (40 mL) along with 2,2-dimethoxypropane (1.1 mL, 9.0 mmol) and p-toluenesulfonic acid monohydrate (0.03 mg, 0.14 mmol) and the resulting composition was refluxed for 6 hours. After cooling, the mixture was neutralized with solid Na₂CO₃ (pH=7), filtered, and concentrated.

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The residue was dissolved in chloroform (50 mL) and washed with water (2x-30 mL). Drying over MgSO_4 and concentrating gave the dimethyl ketal product as an opaque oil (1.4 g, 94%).

5 Part E: Phenol (0.6 g, 6.3 mmol) and cesium carbonate (2.0g, 6.3 mmol) were added to a solution of the dimethyl ketal product (1.4 g, 4.2 mmol) of part D in N,N-dimethylformamide (20 mL). The mixture was heated at 90 degrees Celsius for five
10 hours, diluted with water (20mL), and extracted with ethyl acetate (4x-100 mL). The organic layers were washed with brine (1x-100 mL) and water (1x-100 mL). Concentrating afforded the phenol-O-phenol dimethyl ketal as a dark brown oil (1.51 g, 88%).

15 Part F: To a solution of the phenol-O-phenol dimethyl ketal product (1.5 g, 3.4 mmol) of part E in tetrahydrofuran (10 mL) was added an aqueous lithium hydroxide solution (0.34 g, 14.8 mmol, in 5 mL of H_2O). The reaction was stirred for
20 two hours and then was diluted with water (15 mL) and acidified via 30% HCl_{aq} to pH=3. The acidic solution was extracted with diethyl ether (3x-100 mL). Drying over MgSO_4 and concentrating afforded the carboxylic acid product as a brown oil (1.5 g, quantitative
25 yield).

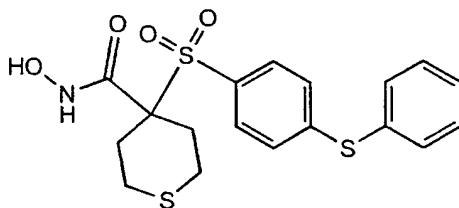
 Part G: To a solution of the carboxylic acid product of Part F (1.3 g, 3.3 mmol) and N-hydroxybenzotriazole hydrate (0.54g, 4.0 mmol) in DMF (15 mL) was added 4-methylmorpholine (1.67 g, 16.5
30 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.2 g, 10.2 mmol), and EDC (0.88 g, 4.6 mmol),

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respectively. After stirring overnight, the DMF was removed *in vacuo* and the residue was taken up in ethyl acetate/water (1:1, 50 mL). The organic layer was washed with brine (1x-20 mL) and water (1x-20 mL) and dried over MgSO_4 . Chromatography (on silica, ethyl acetate/hexane) provided the THP-protected hydroxylamine product as a white solid (0.36 g, 22%) as well as the decarboxylated by-product (0.27 g, 24%).

Part H: To a solution of the THP-protected hydroxylamine product of Part G (0.36 g, 0.73 mmol) in dioxane (3 mL) and methanol (1mL) was added 4 N HCl in dioxane (2 mL). The reaction was stirred for five minutes and then the solvents were removed *in vacuo*. Chromatography (reverse phase C-18, acetonitrile/water) gave the title compound as a white solid (0.13 g, 44%). MS (FAB) M^+H calculated for $\text{C}_{19}\text{H}_{21}\text{NO}_7\text{S}$: 408, found 408.

Example 49: Preparation of tetrahydro-N-hydroxy-4-
[[4-(phenylthio)phenyl]sulfonyl]-2H-
thiopyran-4-carboxamide



25

Part A: To a solution of methyl 2-chloroacetate (322 g, 2.96 mol) in N,N-

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dimethylacetamide (1.0 L) were added thiophenol (400 g, 3.12 mol) and potassium carbonate (408 g, 2.96 mol). The reaction was stirred at ambient temperature overnight (about 18 hours). After
5 diluting with a minimal amount of water (800 mL), the mixture was extracted with ethyl acetate (4x-1L). The organic layers were washed with water (1x-800 mL), dried over MgSO_4 , and concentrated to afford the sulfide product as a clear oil (614 g, quantitative
10 yield).

Part B: To a solution of the sulfide from part A (75.85 g, 0.38 mol) in methanol (1000 mL) was added water (100 mL) and Oxone[®] (720 g, 1.17 mol) at twenty degrees Celsius. An exotherm to 67 degrees
15 Celsius was noted. After two hours, the reaction was filtered and the cake washed well with methanol. The filtrate was concentrated in vacuo. The residue was taken up in ethyl acetate and washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo
20 to give the sulfone as a crystalline solid (82.74 g, 94%).

Part C: To a solution of the sulfone of part B (60.0 g, 258 mmol) in DMA (350 mL) was added the dibromoethylthioether (76.9 g, 310 mmol),
25 followed by potassium carbonate (78.3 g, 568 mmol). The mixture was stirred five minutes before adding catalytic amounts of 4-dimethylaminopyridine and tetrabutylammonium bromide. The reaction was stirred overnight (about 18 hours), after which it was poured
30 into a stirring solution of 10% HCl_{aq} (2.5 L). The resulting precipitate was filtered and washed with

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hexane to remove the excess thioether. Drying *in vacuo* overnight (about 18 hours) yielded the methylester thiopyran -Ph-p-F as a yellow powder (76.1 g, 93%).

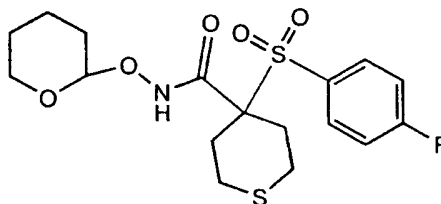
5 Step D: To a solution of the methylester thiopyran -Ph-p-F of part C (4.0 g, 12.6 mmol) in N,N-dimethylacetamide (25 mL) were added cesium carbonate (6.1 g, 18.9 mmol) and thiophenol (2.1 g, 18.9 mmol). The mixture was stirred 2 hours at 90
10 degrees Celsius. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (3x-100 mL). The organic layers were washed with brine (1x-75 mL) and water (1x-75 mL) and was then dried over MgSO₄. Chromatography (on silica, ethyl acetate / hexane)
15 provided the phenyl-S-phenyl methyl ester as a yellowish solid (3.6 g, 71%).

 Step E: Potassium trimethylsilonate (1.24 g, 9.7 mmol) was added to a solution of the phenyl-S-phenyl methyl ester of part D (3.6 g, 8.8 mmol) in
20 tetrahydrofuran (15 mL). The mixture was stirred 2-3 hours at ambient temperature or until a solid precipitate developed. After the hydrolysis was complete, N-methylmorpholine (2.9 mL, 26.4 mmol) was added followed by PyBrop (4.9 g, 10.6 mmol). The
25 solution was stirred for 10 minutes. Aqueous hydroxylamine (0.32 g, 9.7 mmol) was added and the mixture stirred for an additional 2 hours. After completion, the solvent was removed *in vacuo*. Chromatography (reverse phase C-18, acetonitrile /
30 water) of the residue provided the title compound as

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an off white solid (0.82 g, 23%). MS (FAB) M'H
calculated for $C_{18}H_{19}NO_4S_3$: 410, found 410.

Example 50: Preparation of 4-[(4-fluorophenyl)-
sulfonyl]tetrahydro-N-[(tetrahydro-2H-
pyran-2-yl)oxy]-2H-thiopyran-4-
carboxamide



10

Part A: Thiophenol (400 g, 3.12 mol) and
potassium carbonate (408 g, 2.96 mol) were added to a
solution of methyl 2-chloroacetate (322 g, 2.96 mol)
in N,N-dimethylacetamide (1.0 L). The reaction was
15 stirred at ambient temperature overnight (about 18
hours). After diluting with a minimal amount of
water (800 mL), the mixture was extracted with ethyl
acetate (4x-1L). The organic layers were washed with
water (1x-800 mL), dried over $MgSO_4$, and concentrated
20 to afford the sulfide product as a clear oil (614 g,
quantitative yield).

Part B: To a solution of the sulfide from
part A (75.85 g, 0.38 mol) in methanol (1000 mL) was
added water (100 mL) and Oxone[®] (720 g, 1.17 mol) at
25 20 degrees Celsius. An exotherm to 67 degrees
Celsius was noted. After two hours, the reaction was
filtered and the cake was washed well with methanol.

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The filtrate was concentrated *in vacuo*. The residue was taken up in ethyl acetate and washed with brine, dried over MgSO_4 , filtered, and concentrated *in vacuo* to give the methyl ester sulfone as a crystalline solid (82.74 g, 94%).

Part C: To a solution of the methyl ester sulfone product of part B (60.0 g, 258 mmol) in *N,N*-dimethylacetamide (350 mL) was added 2,2-dibromoethylthioether (76.9 g, 310 mmol) followed by potassium carbonate (78.3 g, 568 mmol). The mixture was stirred five minutes before adding catalytic amounts of 4-dimethylaminopyridine and tetrabutylammonium bromide. The reaction was stirred overnight (about 18 hours), after which it was poured into a stirring solution of 10% HCl_{aq} (2.5 L). The resulting precipitate was filtered and washed with hexane to remove the excess thioether. Drying *in vacuo* overnight (about 18 hours) yielded the thiopyran methyl ester as a yellow powder (76.1 g, 93%).

Step D: To a solution of the thiopyran methyl ester of part C (30.0 g, 94 mmol) in tetrahydrofuran (250 mL) was added potassium trimethylsilylate (28.9 g, 226 mmol). The mixture was stirred 2-3 hours at ambient temperature or until a solid precipitate developed. After the hydrolysis was complete, the solvent was removed *in vacuo*. Water (200 mL) was added and the mixture was washed with diethyl ether (1x-200 mL). The aqueous layer was cooled to zero degrees Celsius and 10% HCl_{aq} was slowly added until a precipitate formed. The solid

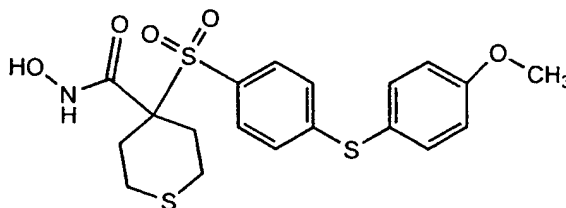
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was collected and dried *in vacuo* with phosphorous pentoxide to afford the thiopyran carboxylic acid as a yellow solid (17.8 g, 62%).

Part E: To a solution of the thiopyran
5 carboxylic acid of part D (17.8 g, 58.5 mmol) in N,N-dimethylformamide (100 mL) was added N-methylmorpholine (19.3 mL, 176 mmol) followed by N-hydroxybenzotriazole hydrate (9.5 g, 70.2 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (10.3 g, 87.8
10 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (16.8 g, 87.8 mmol). The mixture was stirred three hours and was then diluted with water (100 mL). The mixture was extracted with ethyl acetate (4x-200 mL). Organic
15 layers were washed with an aqueous saturated potassium carbonate solution (1x-200 mL), 1% HCl_{aq}, and brine (1x- 200 mL). Drying over MgSO₄ and concentrating *in vacuo* afforded the title compound as an off white solid (30.8 g, quantitative yield). MS
20 (FAB) M⁺H calculated for C₁₇H₂₂FNO₅S₂: 404, found 404.

Example 51: Preparation of Tetrahydro-N-hydroxy-4-
[[4-[(4-methoxyphenyl)thio]phenyl]
sulfonyl]-2H-thiopyran-4-carboxamide

25

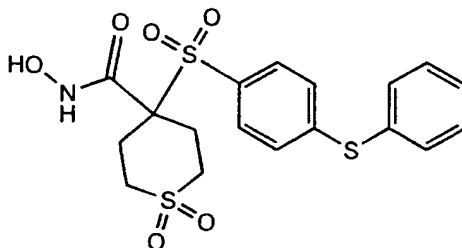


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Part A: To a solution of the title compound of Example 50 (6.0 g, 14.9 mmol) in N,N-dimethylacetamide (25mL) was added 4-methoxy thiophenol (2.5 g, 17.8 mL), followed by potassium carbonate (6.2 g, 44.7 mmol). The reaction was heated at 60 degrees Celsius for three hours. The reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (4x-100 mL). The organic layers were washed with water (2x-50 mL) and dried over MgSO₄. Concentrating in vacuo provided the THP-protected - Phenyl -S- pPhenyl-OMe product as a yellowish solid (9.2 g, quantitative yield).

Part B: To a solution of the THP-protected - Phenyl -S- pPhenyl-OMe product from part A (9.2 g, 14.9 mmol) in dioxane was slowly added 4N HCl in dioxane (10 mL). After stirring overnight (about 18 hours), the solvent was removed. Chromatography on the resultant residue (reverse phase C-18, acetonitrile/water) gave the title compound as a white solid (1.84 g, 28.3%). MS (FAB) M⁺H calculated for C₁₉H₂₁NO₅S₃: 440, found 440.

Example 52: Preparation of Tetrahydro-N-hydroxy-4-[(4-phenylthio)phenyl]sulfonyl]-2H-thiopyran-4-carboxamide 1,1-dioxide



Part A: To a solution of the title compound of Example 50 (13.0 g, 24.5 mmol) in methylene chloride (100 mL) cooled to zero degrees Celsius was slowly added 50-60% m-chloroperbenzoic acid (17.1 g, 49.5 mmol). The mixture was stirred one hour at zero degrees Celsius followed by an additional 3 hours as the temperature rose to ambient conditions. Water (200 mL) was added and the mixture was neutralized with 10% ammonium hydroxide (100 mL) and dried layer was washed with water (1x-200 mL) and dried over MgSO_4 . Concentrating in vacuo provided an orangish oil (3.5 g, 33%). The water/10% ammonium hydroxide solution was saturated with sodium chloride and extracted with ethyl acetate (2x-400 mL). Organic layer was dried over MgSO_4 and concentrated to afford the THP-protected sulfone-thiopyran-p-F compound as an orange foam (6.1 g, 57%).

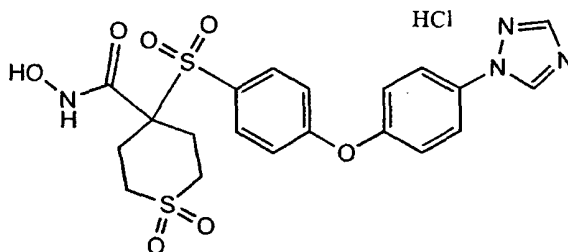
Part B: To a solution of the THP-protected sulfone-thiopyran-p-F from Part A (9.6 g, 22 mmol) in N,N-dimethylacetamide (120 mL) was added thiophenol (2.9 g, 26.4 mL), followed by potassium carbonate (9.1 g, 66 mmol). The reaction was heated at 60 degrees Celsius for four hours. The reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (4x-100 mL). The organic layers were washed with water (2x-50 mL) and dried over MgSO_4 . Chromatography (on silica, ethyl acetate/hexane) provided the THP-protected -phenyl-S-phenyl product as an orange oil (5.1 g, 43%).

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Part C: To a solution of the THP-protected
-phenyl-S-phenyl product from part B (5.1 g, 9.4
mmol) in dioxane was slowly added 4N HCl in dioxane
(10 mL). After stirring overnight (about 18 hours),
5 the solvent was removed. Chromatography of the
resultant residue (reverse phase C-18,
acetonitrile/water) gave the title compound as a pink
solid (1.2 g, 29%). MS (FAB) M⁺H calculated for
C₁₈H₁₉NO₆S₃: 442, found 442.

10

Example 53: Preparation of Tetrahydro-N-hydroxy-4-
[[4-[4-(1H-1,2,4-triazol-1-yl)
phenoxy]-phenyl]-sulfonyl]-2H-thiopyran-
4-carboxamide 1,1-dioxide,
15 monohydrochloride



Part A: To a solution of the title compound
20 of Example 50 (13.0 g, 24.5 mmol) in methylene
chloride (100 mL) cooled to zero degrees Celsius was
slowly added 50-60% m-chloroperbenzoic acid (17.1 g,
49.5 mmol). The mixture was stirred one hour at zero
degrees Celsius followed by an additional 3 hours as
25 the temperature rose to ambient conditions. Water
(200 mL) was added and the mixture was neutralized
with 10% ammonium hydroxide (100 mL). The organic

-402-

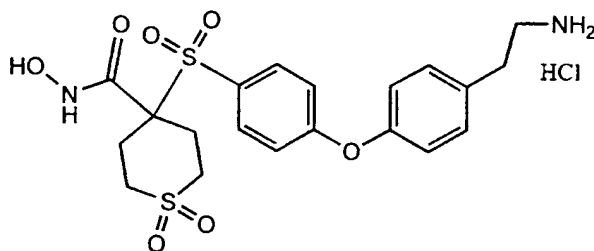
layer was washed with water (1x-200 mL) and dried over MgSO_4 . Concentrating in vacuo provided an orangish oil (3.5 g, 33%). The water/10% ammonium hydroxide solution was saturated with sodium chloride and extracted with ethyl acetate (2x-400 mL). Organic layer was dried over MgSO_4 and concentrated to afford the THP-protected sulfone-thiopyran-p-F as an orange foam (6.1 g, 57%).

Part B: To a solution of the THP-protected sulfone-thiopyran-p-F from A (6.0 g, 13.8 mmol) in *N,N*-dimethylformamide (25 mL) was added 4-(1H-1,2,4-triazol-1-yl)phenol (4.4 g, 27.5 mmol), followed by cesium carbonate (13.4 g, 41.4 mmol). The reaction was heated at 95 degrees Celsius for five hours. The reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (4x-100 mL). The organic layers were washed with water (2x-50 mL) and dried over MgSO_4 . Concentrating afforded the THP-protected phenyl-O-phenyl triazole product as a tan solid (9.7 g, quantitative yield).

Part C: To a solution of the crude THP-protected phenyl-O-phenyl triazole product from B (8.0 g, 13.8 mmol) in acetonitrile (40 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a tan solid (1.3 g, 18%). MS (FAB) M^+H calculated for $\text{C}_{20}\text{H}_{21}\text{ClN}_4\text{O}_7\text{S}_2$: 493, found 493.

-403-

Example 54: Preparation of 4-[[4-[4-(2-aminoethyl))-
phenoxy]phenyl]sulfonyl]tetrahydro-N-
hydroxy-2H-thiopyran-4-carboxamide 1,1-
dioxide monohydrochloride



5

Part A: To a solution of the title compound
of Example 50 (13.0 g, 24.5 mmol) in methylene
chloride (100 mL) cooled to zero degrees Celsius was
10 slowly added 50-60% m-chloroperbenzoic acid (17.1 g,
49.5 mmol). The mixture was stirred one hour at zero
degrees Celsius followed by an additional 3 hours as
the temperature rose to ambient conditions. Water
(200 mL) was added and the mixture was neutralized
15 with 10% ammonium hydroxide (100 mL). The organic
layer was washed with water (1x-200 mL) and dried
over MgSO₄. Concentrating *in vacuo* provided an
orangish oil (3.5 g, 33%). The water/10% ammonium
hydroxide solution was saturated with sodium chloride
20 and extracted with ethyl acetate (2x-400 mL). The
organic layer was dried over MgSO₄ and concentrated to
afford the THP-protected sulfone-thiopyran-p-F as an
orange foam (6.1 g, 57%).

Part B: To a solution of the THP-protected
25 sulfone-thiopyran-p-F from A (6.0 g, 13.8 mmol) in
N,N-dimethylacetamide (25 mL) was added tyramine (3.8
g, 28 mmol) followed by cesium carbonate (13.6 g, 42

-404-

mmol). The reaction was heated at 95 degrees Celsius for five hours. Removing the N,N-dimethylacetamide *in vacuo* afforded a brown solid (20 g).

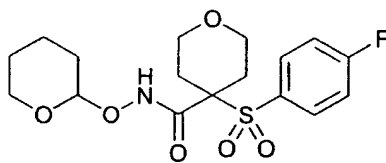
Chromatography (reverse phase, C-18,

5 acetonitrile/water) gave the THP-protected tyramine product as a tan oil (1.0 g, 13%).

Part C: To a solution of the crude THP-protected tyramine product from part B (1.0 g, 1.8 mmol) in acetonitrile (40 mL) was slowly added 10%
10 HCl_{aq} (100 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a tan solid (0.9 g, 99%). MS (FAB) M⁺H calculated for C₂₀H₂₅ClN₂O₇S₂: 469, found 469.

15

Example 55: Preparation of 4-[(4-fluorophenyl)-sulfonyl]tetrahydro-N-[(tetrahydro-2H-pyran-2-yl)oxyl]-2H-pyran-4-carboxamide



20

Part A: In dry equipment under nitrogen, sodium metal (8.97 g, 0.39 mol) was added to methanol (1000 mL) at two degrees Celsius. The reaction was
25 stirred at ambient temperature for forty five minutes at which time the sodium had dissolved. The solution was chilled to five degrees Celsius and p-fluorothiophenol (41.55 mL, 0.39 mmol) was added,

-405-

followed by methyl 2-chloroacetate (34.2 mL, 0.39 mol). The reaction was stirred at ambient temperature for four hours, filtered, and concentrated *in vacuo* to give the sulfide as a clear
5 colorless oil (75.85 g, 97%).

Part B: To a solution of the sulfide from part A (75.85 g, 0.38 mol) in methanol (1000 mL) were added water (100 mL) and Oxone[®] (720 g, 1.17 mol) at 20 degrees Celsius. An exotherm to 67 degrees
10 Celsius was noted. After two hours, the reaction was filtered and the cake was washed well with methanol. The filtrate was concentrated *in vacuo*. The residue was taken up in ethyl acetate and washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*
15 to give the sulfone as a crystalline solid (82.74 g, 94%).

Part C: To a solution of the sulfone from part B (28.5 g, 0.123 mol) in N,N-dimethylacetamide (200 mL) were added potassium carbonate (37.3 g, 0.27
20 mol), bis-(2-bromoethyl)ether (19.3 mL, 0.147 mol), 4-dimethylaminopyridine (0.75 g, 6 mmol), and tetrabutylammonium bromide (1.98 g, 6 mmol). The reaction was stirred overnight (about 18 hours) at ambient temperature. The reaction was slowly poured
25 into 1N HCl (300 mL), the resultant solid filtered and the cake washed well with hexanes. The solid was recrystallized from ethyl acetate/hexanes to give the pyran compound as a beige solid (28.74 g, 77%). MS (ES+) MH⁺ calculated for C₁₃H₁₅O₅S₁F₁, 303, found 303.

30 Part D: In dry equipment under nitrogen, the pyran compound from part C (8.0 g, 26.5 mmol) was

-406-

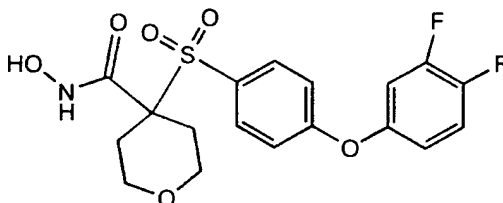
dissolved in dry tetrahydrofuran (250 mL) and a solution of potassium trimethylsilonate (10.2 g, 79.5 mmol) in dry tetrahydrofuran (15 mL) was added at ambient temperature. After ninety minutes, water (100 mL) was added and the solution concentrated in vacuo. The residue was taken up in water and extracted with ethyl acetate to remove unreacted starting material. The aqueous solution was treated with 6N HCl until pH=1. The slurry was extracted with ethyl acetate and the combined extracts washed with water, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was heated in diethyl ether, the solid filtered and dried to give the carboxylic acid as a crystalline solid (5.78 g, 76%). HRMS (ES-) M-H calculated for C₁₂H₁₃O₅ S₁F₁: 287.04, found 287.04.

Part E: In dry equipment under nitrogen, the carboxylic acid from part D (9.1g, 31.6 mmol) was dissolved in dry N,N-dimethylformamide (70 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (5.1 g, 37.9 mmol), N-methylmorpholine (10.4 mL, 94.8 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (11.5 g, 98 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.48 g, 44.2 mmol). After three hours at ambient temperature, the reaction was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with water, 5% KHSO₄, saturated NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Chromatography (on silica, ethyl acetate/hexanes) provided the title compound as a crystalline solid (9.7 g, 80%). HRMS

-407-

(ES+) MH⁺ calculated for C₁₇H₂₂NO₆ S₁F₁: 388.12, found 388.12.

Example 56: Preparation of 4-[[4-(3,4-difluorophenoxy)-phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



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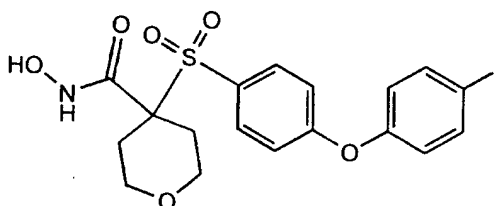
Part A: To a solution of the title compound of Example 55 (2.0 g, 5.2 mmol) in N,N-dimethylacetamide (6 mL) was added 3,4-difluorophenol (1.0 g, 7.7 mmol), followed by cesium carbonate (6.6 g, 20.2 mmol). The reaction was heated at 95 degrees Celsius for five hours. Removing the N,N-dimethylacetamide *in vacuo* afforded a brown solid (8.3 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected difluoro product in solution.

Part B: To the collected THP-protected difluoro product from A in acetonitrile/ water (50 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a white

-408-

solid (1.02 g, 48.6%). MS (FAB) M'H calculated for $C_{18}H_{17}FNO_6S$: 414, found 414.

Example 57: Preparation of Tetrahydro-N-hydroxy-
4-[[4-(4-iodophenoxy) phenyl]sulfonyl]-
2H-pyran-4-carboxamide

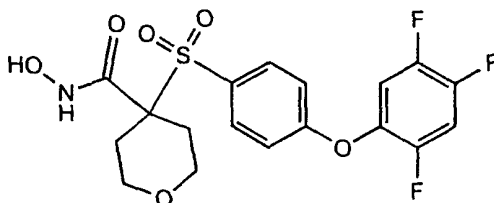


Part A: To a solution of the title compound of Example 55 (2.0 g, 5.2 mmol) in N,N-dimethylacetamide (6 mL) was added 4-iodophenol (1.7 g, 7.8 mmol), followed by cesium carbonate (6.6 g, 20.2 mmol). The reaction was heated at 95 degrees Celsius for five hours. Removing the N,N-dimethylacetamide in vacuo afforded a brown solid (5.7 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected iodo product in solution.

Part B: To the solution of the crude THP-protected iodo product from A in acetonitrile/water (40 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a white solid (2.6 g, 99%). MS (FAB) M'H calculated for $C_{18}H_{18}INO_6S$: 504, found 504.

Example 58: Preparation of Tetrahydro-N-hydroxy-4-
[[4-(2,4,5-trifluorophenoxy)phenyl]-
sulfonyl]-2H-pyran-4-carboxamide

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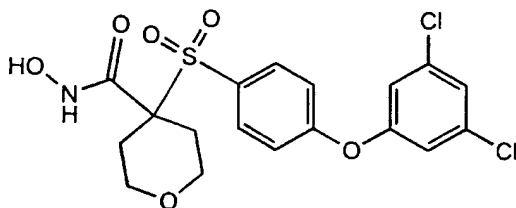


Part A: To a solution of the title compound of Example 55 (2.0 g, 5.2 mmol) in N,N-dimethylacetamide (6 mL) was added 2,4,5-trifluorophenol (1.2 g, 7.8 mmol), followed by cesium carbonate (10.1 g, 31.0 mmol). The reaction was heated at 95 degrees Celsius for thirty-two hours. Removing the N,N-dimethylacetamide in vacuo afforded a brown solid (5.7 g, quantitative). Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP-protected phenol product (1.2 g, 44%).

Part B: To the solution of the crude THP-protected phenol product from Part A (1.2 g, 2.3 mmol) in acetonitrile/water (40 mL) was slowly added 10% HCl_{aq} (100 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a white solid (0.79 g, 79%). MS (FAB) M⁺H calculated for C₁₈H₁₆F₃NO₆S: 430, found 430.

Example 59: Preparation of 4-[[4-(3,5-dichlorophenoxy)-phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide

5

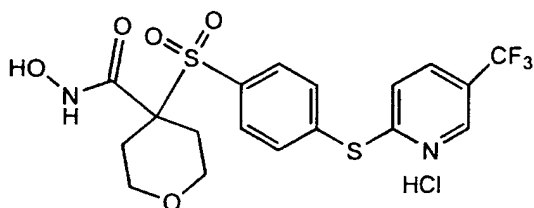


Part A: To a solution of the title compound of Example 55 (2.0 g, 5.2 mmol) in N,N-dimethylacetamide (6 mL) was added 3,5-dichlorophenol (1.3 g, 7.8 mmol), followed by cesium carbonate (6.6 g, 20.2 mmol). The reaction was heated at 95 degrees Celsius for twelve hours. Removing the N,N-dimethylacetamide in vacuo afforded a brown solid (5.7 g, quantitative). The residue was taken up in acetonitrile/water (20 mL) and acidified to pH=6. A white precipitate formed and was collected affording the THP-protected product as a white cake (1.8 g, 64%).

Part B: To the THP-protected product from Part A (1.8 g, 3.4 mmol) in acetonitrile/water (20 mL) was slowly added 10% HCl_{aq} (40 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a white solid (0.71 g, 47%). MS (FAB) M⁺H calculated for C₁₈H₁₇Cl₂NO₆S: 447, found 447.

-411-

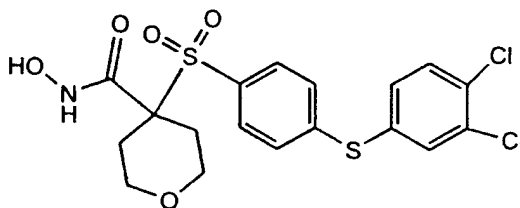
Example 59: Preparation of Tetrahydro-N-hydroxy- 4-
[[4-[[5-(trifluoromethyl)-2-pyridinyl]-
thio]phenyl]sulfonyl]-2H-pyran-4-
5 carboxamide monohydrochloride



Part A: To a solution of the title compound
10 of Example 55 (2.0 g, 5.2 mmol) in N,N-
dimethylacetamide (6 mL) was added 5-
(trifluoromethyl)-2-pyridinyl thiophenol (1.4 g, 7.8
mmol), followed by potassium carbonate (2.2 g, 15.6
mmol). The reaction was heated at 65 degrees Celsius
15 for twelve hours. Removing the N,N-dimethylacetamide
in vacuo afforded a brown solid (5.4 g,
quantitative). Chromatography (reverse phase, C-18,
acetonitrile/water) gave the THP-protected product in
solution.

20 Part B: To the solution of the crude THP-
protected product from Part A in acetonitrile/water
(40 mL) was slowly added 10% HCl_{aq} (40 mL). After
stirring overnight (about 18 hours), the acetonitrile
was removed. The resultant precipitate was
25 collected, giving the title compound as a white solid
(0.20 g, 8%). MS (FAB) M⁺H calculated for
C₁₈H₁₇F₃N₂O₅S₂: 463, found 463.

Example 60: Preparation of 4-[[4-(3,4-
dichlorophenyl)-thio]phenyl]sulfonyl]-
tetrahydro-N-hydroxy-2H-pyran-4-
5 carboxamide



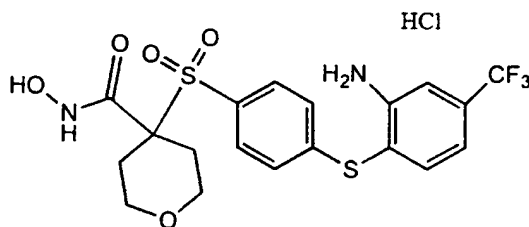
Part A: To a solution of the title compound
10 of Example 55 (2.0 g, 5.2 mmol) in N,N-
dimethylacetamide (6 mL) was added 3,4-
dichlorothiophenol (1.4 g, 7.8 mmol) followed by
potassium carbonate (2.2 g, 15.6 mmol). The reaction
was heated at 70 degrees Celsius for six hours.
15 Removing the N,N-dimethylacetamide *in vacuo* afforded
a brown solid (5.6 g, quantitative). Chromatography
(reverse phase, C-18, acetonitrile/water) gave the
THP protected product in solution.

Part B: To the solution of the THP-
20 protected product from Part A in acetonitrile/water
(40 mL) was slowly added 10% HCl_{aq} (40 mL). After
stirring overnight (about 18 hours), the acetonitrile
was removed. The resultant precipitate was
collected, giving the title compound as a white solid
25 (1.5 g, 62%). MS (FAB) M⁺H calculated for C₁₈H₁₇Cl₂NO₅S:
463, found 463.

-413-

Example 61: Preparation of 4-[[4-[[2-amino-4-(trifluoromethyl)phenyl]thio]phenyl]-sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide, monohydrochloride

5



Part A: To a solution of the title compound of Example 55 (2.0 g, 5.2 mmol) in N,N-dimethylacetamide (6 mL) was added 2-amino-4-(trifluoromethyl)thiophenol hydrochloride (1.8 g, 7.8 mmol), followed by potassium carbonate (3.6 g, 26 mmol). The reaction was heated at 70 degrees Celsius for eight hours. Removing the dimethylacetamide in vacuo afforded a brown solid (14 g, quantitative).

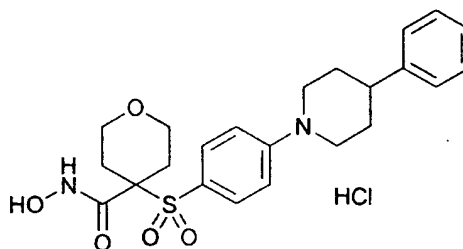
15 Chromatography (reverse phase, C-18, acetonitrile/water) gave the THP protected product in solution.

Part B: To the solution of the THP-protected product in acetonitrile / water (40 mL) was slowly added 10% HCl_{aq} (40 mL). After stirring overnight (about 18 hours), the acetonitrile was removed. The resultant precipitate was collected, giving the title compound as a white solid (1.3 g, 52%). MS (FAB) M⁺H calculated for C₁₈H₁₇Cl₂NO₆S: 477, found 477.

25

-414-

Example 62: Preparation of Tetrahydro-4[[4-(4-phenyl-1-piperidinyl)phenyl]sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride



5

Part A: In dry equipment under nitrogen, sodium metal (8.97 g, 0.39 mol) was added to methanol (1000 mL) at two degrees Celsius. The reaction was stirred at ambient temperature for forty-five minutes at which time the sodium had dissolved. The solution was chilled to five degrees Celsius and p-fluorothiophenol (41.55 mL, 0.39 mmol) was added, followed by methyl 2-chloroacetate (34.2 mL, 0.39 mol). The reaction was stirred at ambient temperature for four hours, filtered, and concentrated *in vacuo* to give the sulfide as a clear colorless oil (75.85 g, 97%).

Part B: To a solution of the sulfide from part A (75.85 g, 0.38 mol) in methanol (1000 mL) was added water (100 mL) and Oxone® (720 g, 1.17 mol) at 20 degrees Celsius. An exotherm to 67 degrees Celsius was noted. After two hours, the reaction was filtered and the cake was washed well with methanol. The filtrate was concentrated *in vacuo*. The residue was taken up in ethyl acetate and washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*.

-415-

to give the sulfone as a crystalline solid (82.74 g, 94%).

Part C: To a solution of the sulfone from part B (28.5 g, 0.123 mol) in N,N-dimethylacetamide (200 mL) were added potassium carbonate (37.3 g, 0.27 mol), bis-(2-bromoethyl)ether (19.3 mL, 0.147 mol), 4-dimethylaminopyridine (0.75 g, 6 mmol), and tetrabutylammonium bromide (1.98 g, 6 mmol). The reaction was stirred overnight (about 18 hours) at ambient temperature. The reaction was slowly poured into 1N HCl (300 mL), the resultant solid filtered and the cake washed well with hexanes. The solid was recrystallized from ethyl acetate/hexanes to give the pyran compound as a beige solid (28.74 g, 77%). MS (ES+) MH⁺ calculated for C₁₃H₁₅O₅S₁F₁: 303, found 303.

Part D: To a solution of the pyran compound from part C (1.21 g, 4.0 mmol) in dimethyl sulfoxide (10 mL) were added cesium carbonate (3.26 g, 10 mmol) and 4-phenylpiperidine (0.64 g, 4.0 mmol) in methyl sulfoxide (10 mL). The slurry was stirred at 90 degrees Celsius for two hours. The reaction was cooled, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with 5% KHSO₄, saturated NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The resultant solid was slurried in diethyl ether, filtered and dried to give the N-substituted piperidine as a white solid (1.2 g, 67%). MS (FAB+) MH⁺ calculated for C₂₄H₂₉N₁O₅S₁: 444, found 444.

Part E: To a slurry of the N-substituted piperidine from part D (815 mg, 1.84 mmol) in

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methanol (5 mL) and tetrahydrofuran (5 mL) was added 50% sodium hydroxide (3 mL). After twenty-four hours at ambient temperature, the reaction was concentrated *in vacuo*. The slurry was diluted with water (10 mL) and 6N HCl was added until the pH=7. Vacuum filtration of the resulting precipitate provided the acid as a white solid (705 mg, 89%). MS (FAB+) MH⁺ calculated for C₂₃H₂₇N₁O₅S₁: 430, found 430.

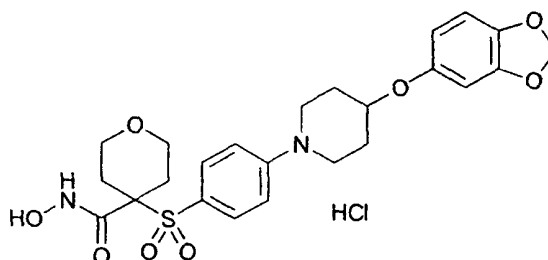
Part F: In dry equipment under nitrogen, the carboxylic acid from part E (620 mg, 1.44 mmol) was slurried in methylene chloride (10 mL) and N,N-dimethylformamide (3 mL) and the remaining reagents were added to the slurry in the following order: bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (810 mg, 1.73 mmol), N-methylmorpholine (0.5 mL, 4.34 mmol), and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (190 mg, 1.59 mmol). After four hours at ambient temperature, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP-protected hydroxamate as a white solid (630 mg, 83%). MS (FAB+) MH⁺ calculated for C₂₈H₂₂N₂O₆ S₁: 529, found 529.

Part G: To a slurry of the THP-protected hydroxamate from part F (600 mg, 1.14 mmol) in dioxane (1.5 mL) was added a 4N HCl dioxane solution (1.5 mL) and methanol (1.5 mL). After two hours at ambient temperature the reaction was poured into diethyl ether (100 mL). Vacuum filtration of the

-417-

resulting precipitate provided the title compound as a light beige solid (500 mg, 91%). MS (FAB+) M+Li calculated for $C_{23}H_{28}N_2O_5S_1$, 445, found 445.

- 5 Example 63: Preparation of 4-[[4-[4-(1,3-Benzodioxol-5-yloxy)-1-piperidinyl]phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-
carboxamide, monohydrochloride



Part A: In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL,
15 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below 30 degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was
20 taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: In dry equipment under nitrogen,
25 the BOC piperidine from part A (5.0 g, 24.8 mmol) in dry tetrahydrofuran (100 mL) was cooled to zero

degrees Celsius and triphenylphosphine (9.77 g, 37.3 mmol) was added. After fifteen minutes of stirring at zero degrees Celsius, sesamol (5.15 g, 37.3 mmol) was added to the reaction followed by the dropwise
5 addition of diethylazodicarboxylate (5.87 mL, 37.7 mmol). The reaction was stirred for thirty minutes at zero degrees Celsius and then at ambient temperature for twenty hours. The reaction was concentrated *in vacuo*. The residue was slurried in
10 diethyl ether, the triphenyl phosphine oxide filtered off and the filtrate concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted BOC piperidine as a white solid (3.14 g, 39%).

15 Part C: To a slurry of the substituted BOC piperidine from part B (3.14 g, 9.8 mmol) in dioxane (15 mL) was added a 4N HCl dioxane solution (15 mL). After three hours at ambient temperature, the reaction was concentrated *in vacuo*. The residue was
20 slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the hydrochloride salt as a white solid (2.3 g, 100%).

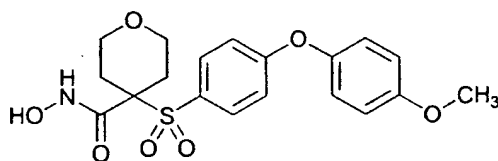
Part D: To a slurry of the hydrochloride salt from part C (0.93 g, 3.6 mmol) in N,N-
25 dimethylformamide (10 mL) were added cesium carbonate (2.93 g, 9 mmol) and the title compound of Example 55 (1.16 g, 3.0 mmol). The slurry was stirred at 90 degrees Celsius for twenty four hours. The reaction was concentrated *in vacuo*. The residue was taken up
30 in ethyl acetate, washed with water, 5% KHSO₄, saturated NaHCO₃, brine, dried over Na₂SO₄, filtered,

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and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a white solid (640 mg, 36%). MS (FAB+) MH⁺ calculated for C₂₉H₃₆N₂O₉ S₁: 589, found 589.

Part E: To a slurry of the THP-protected hydroxamate from part D (600 mg, 1.02 mmol) in dioxane (3 mL) were added a 4N HCl dioxane solution (3 mL) and methanol (3 mL). After one hour at ambient temperature, the reaction was poured into diethyl ether (100 mL). Vacuum filtration of the resulting precipitate provided the title compound as a light beige solid (440 mg, 80%). HRMS (ES+) MH⁺ calculated for C₂₄H₂₈N₂O₈ S₁: 505.16, found 505.16.

Example 64: Preparation of Tetrahydro-N-hydroxy-4-[[4-(4-methoxyphenoxy)phenyl]sulfonyl]-2H-pyran-4-carboxamide



20

Part A: To a solution of the title compound of Example 55 (3.48 g, 9 mmol) in N,N-dimethylformamide (20 mL) were added cesium carbonate (8.8 g, 27 mmol) and p-methoxyphenol (2.23 g, 18 mmol). The slurry was stirred at 95 degrees Celsius for twenty four hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate,

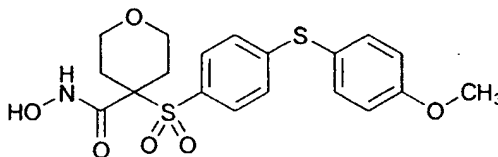
-420-

washed with brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a beige foam (3.82 g, 86%).

5 MS (FAB+) MH^+ calculated for $\text{C}_{24}\text{H}_{29}\text{N}_1\text{O}_8$ S_1 : 492, found 492.

Part B: To a slurry of the THP-protected hydroxamate from part A (3.6 g, 7.33 mmol) in dioxane (18 mL) were added a 4N HCl dioxane solution (18 mL)
10 and methanol (18 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give
15 the title compound as a white solid (2.1 g, 70%).
HRMS (ES+) MH^+ calculated for $\text{C}_{19}\text{H}_{21}\text{N}_1\text{O}_7\text{S}_1$: 408.11, found 408.11.

Example 65: Preparation of Tetrahydro-N-hydroxy-4-
20 [[4-(4-methoxyphenylthio)phenyl]-
sulfonyl]-2H-pyran-4-carboxamide



25 Part A: To a solution of the title compound of Example 55 (3.1 g, 8 mmol) in *N,N*-dimethylformamide (20 mL) were added potassium carbonate (1.33 g, 9.6 mmol) and *p*-

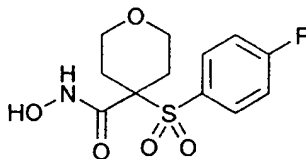
-421-

methoxybenzenethiol (1.48 mL, 12 mmol). The slurry was stirred at 65 degrees Celsius for twenty-four hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with
5 brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a white foam (4.1 g, 100%). HRMS (ES+) $\text{M}+\text{NH}_4^+$ calculated for $\text{C}_{24}\text{H}_{29}\text{N}_1\text{O}_7\text{S}_2$: 525.17, found
10 525.17.

Part B: To a slurry of the THP-protected hydroxamate from part A (4.0 g, 7.9 mmol) in dioxane (20 mL) was added a 4N HCl dioxane solution (20 mL) and methanol (20 mL). After fifteen minutes at
15 ambient temperature, the reaction was diluted with ethyl acetate, washed with water, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (2.21 g, 67%). HRMS (ES+) MH^+ calculated for $\text{C}_{19}\text{H}_{21}\text{N}_1\text{O}_6\text{S}_2$: 424.09, found 424.09.
20

Example 66: Preparation of 4-[(4-fluorophenyl)-sulfonyl]tetrahydro-N-hydroxy-2H-
pyran-4-carboxamide

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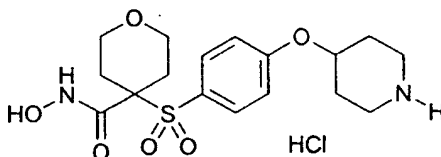


-422-

Part A: To a slurry of the title compound of Example 55 (530 mg, 1.38 mmol) in dioxane (5 mL) was added a 4N HCl dioxane solution (5 mL) and methanol (5 mL). After fifteen minutes at ambient
5 temperature the reaction was concentrated *in vacuo*. Reverse phase chromatography (on silica, acetonitrile/water) provided the title compound as a beige solid (140 mg, 34%). HRMS (ES+) $M + NH_4^+$ calculated for $C_{12}H_{14}N_1O_5S_1F_1$: 321.09, found 321.09.

10

Example 67: Preparation of tetrahydro-N-hydroxy-4-
[[4-(4-piperidinyloxy)phenyl]sulfonyl]-
2H-pyran-4-carboxamide, monohydrochloride



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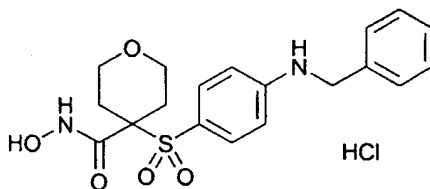
Part A: In dry equipment under nitrogen, 4-hydroxy-N-t-(butoxycarbonyl)piperidine (844 mg, 4.2 mmol) was added to 60% sodium hydride (210 mg, 5.25
20 mmol) in dry N,N-dimethylformamide (10 mL) at zero degrees Celsius. The slurry was stirred for two hours at ambient temperature. At five degrees Celsius, the title compound of Example 55 (1.35 g, 3.5 mmol) was added and the reaction heated to 50 degrees
25 Celsius for three hours. The reaction was cooled, quenched with water, and concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na₂SO₄, filtered, and concentrated

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in vacuo. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a white foam (283 mg, 14%). MS (FAB+) MH⁺ calculated for C₂₇H₄₀N₂O₉S₁: 569, found 569.

Part B: To a slurry of the THP-protected hydroxamate from part A (530 mg, 0.93 mmol) in dioxane (5 mL) were added a 4N HCl dioxane solution (5 mL) and methanol (5 mL). After fifteen minutes at ambient temperature the reaction was concentrated in vacuo. Reverse phase chromatography (on silica, acetonitrile /water buffered with 0.01% HCl) provided the title compound as a beige solid (240 mg, 62%). HRMS (ES+) MH⁺ calculated for C₁₇H₂₄N₂O₆S₁: 385.14, found 385.14.

Example 68: Preparation of tetrahydro-N-hydroxy-4-[[4-[(4-phenylmethyl)amino]phenyl]-sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride

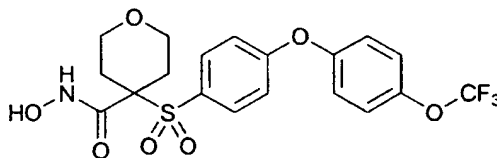


Part A: In a solid phase reaction vessel, benzylamine (11.0 mL, 100 mmol) was added to Resin II (in a procedure described hereinafter; 5.0 g, 4.55 mmol) swollen in dry 1-methyl-2-pyrrolidinone (40 mL). The reaction was heated to 100 degrees Celsius

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for forty-eight hours with good shaking. The resin was transferred to a frit and washed four times with N,N-dimethylformamide (30 mL), four times with methanol (30 mL), four times with methylene chloride (30 mL), and dried. The dried resin was transferred to a flask and a solution of 95% trifluoroacetic acid/5%water (50 mL) was added. The slurry was stirred for one hour, filtered and the cake was washed with methylene chloride. The combined filtrates were concentrated in vacuo. The residue was dissolved in ethyl acetate and saturated sodium bicarbonate solution was added until pH=7. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. Reverse phase chromatography (on silica, acetonitrile/water buffered with 0.01% HCl) provided the title compound as a reddish solid (1.01 g, 52%). HRMS (ES+) M+ NH₄⁺ calculated for C₁₉H₂₂N₂O₅S₁: 408.16, found 408.16.

Example 69: Preparation of Tetrahydro-N-hydroxy-4-[[4-[4-trifluoromethoxy)phenoxy)phenyl]-sulfonyl]-2H-pyran-4-carboxamide



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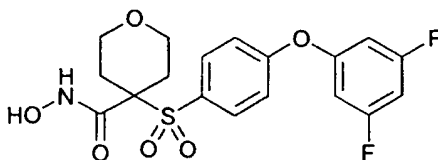
Part A: To a solution of the title compound of Example 55 (3.1 g, 8 mmol) in N,N-dimethylacetamide (20 mL) were added cesium carbonate

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(8.8 g, 27 mmol) and p-(trifluoromethoxy)phenol (2.1 mL, 16 mmol). The slurry was stirred at 95 degrees Celsius for nineteen hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a white foam (4.2 g, 96%). HRMS (ES+) MH⁺ calculated for C₂₄H₂₆N₁O₈ S₁F₃: 546.14, found 546.14.

Part B: To a slurry of the THP-protected hydroxamate from part A (4.0 g, 7.3 mmol) in dioxane (20 mL) were added a 4N HCl dioxane solution (20 mL) and methanol (20 mL). After fifteen minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (2.2 g, 65%). HRMS (ES+) M⁺ NH₄⁺ calculated for C₁₉H₁₈N₁O₇S₁F₃: 479.11, found 479.11.

Example 70: Preparation of 4-[[4-(3,5-difluorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: To a solution of the title compound of Example 55 (3.1 g, 8 mmol) in N,N-dimethylacetamide (20 mL) were added cesium carbonate (8.8 g, 27 mmol) and 3,5-difluorophenol (2.1 g, 16 mmol). The slurry was stirred at 95 degrees Celsius for forty-eight hours. The reaction was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted THP-protected hydroxamate as a beige foam (3.23 g, 81%). HRMS (ES+) MH⁺ calculated for C₂₃H₂₅N₁O₇ S₁F₂: 498.14, found 498.14.

Part B: To a slurry of the THP-protected hydroxamate from part A (3.2 g, 6.3 mmol) in dioxane (20 mL) were added a 4N HCl dioxane solution (20 mL) and methanol (20 mL). After fifteen minutes at ambient temperature the reaction was diluted with ethyl acetate and washed with water, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the title compound as a white solid (1.5 g, 57%). HRMS (ES+) M⁺ NH₄⁺ calculated for C₁₈H₁₇N₁O₆ S₁F₂: 431.11, found 431.11.